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EDITORIAL

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ABOUT COVER

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AIMS AND SCOPE

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

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EDITORIAL

Cancer recognition of artificial intelligence

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Abstract

The recognition mechanism of artificial intelligence (AI) is an interesting topic in understanding AI neural networks and their application in therapeutics. A number of multilayered neural networks can recognize cancer through deep learning. It would be interesting to think about whether human insights and AI attention are associated with each other or should be translated, which is one of the main points in this editorial. The automatic detection of cancer with computer-aided diagnosis is being applied in the clinic and should be improved with feature mapping in neural networks. The subtypes and stages of cancer, in terms of progression and metastasis, should be classified with AI for optimized therapeutics. The determination of training and test data during learning and selection of appropriate AI models will be essential for therapeutic applications.

Key Words: Artificial intelligence; Cancer; Network; Recognition; Therapeutic application

Core Tip: Recently, rapidly growing advances in deep learning have enabled cancer recognition by artificial intelligence (AI). Differences between human insights and AI attention may exist, and the interpretation of the modeling would lead to the further progression of AI-oriented therapeutics. The massive ability of AI is useful for cancer recognition.

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INTRODUCTION

The automatic detection of cancer has already been in practice and will become generalized[1]. Computer-aided diagnosis (CAD) is growing, and the detection and classification of cancer has been achieved in the identification of the subtypes of leukemia with dense convolutional neural networks and residual convolutional neural networks[1]. A CAD system with a massive artificial neural network based on the soft tissue technique detected lung cancer in X-ray images[2]. Infection of *Helicobacter pylori* was predicted with endoscopic images by artificial intelligence (AI)[3]. A faster region-based convolutional neural network was applied to diagnose the T stage of gastric cancer in enhanced computed tomography (CT) images of gastric cancer[4]. Digital images of pathological data in cancer have been utilized in cancer diagnosis[5]. Digital pathology using whole-slide images may contribute into the "remote" assessment[6]. Automated image analysis and AI applications are increasing in the field of thyroid pathology[7]. Cancer recognition by AI has become more accurate and precise, accompanied by the progress of neural networks and calculation capacity[8]. It is time to think of ways to manage teaching AI in cancer therapeutics[9].

RECOGNITION AND AI APPLICATION

It may be possible that deep learning approaches such as a pretrained biomedical text mining model in natural language corpora apply to the recognition of cancer by AI[10]. The concept of the adversarial nets framework has advanced the field of recognition[11]. The recognition mechanism of AI application can be translated to human language *via* the indication of attention[12]. Future perspectives on cancer recognition in AI may need to focus on the translation of AI and human languages. Liver cancer survival can be predicted with deep learning-based multiomics integration[13]. Autoencoder architecture was used to integrate RNA sequencing (RNA-Seq) data, DNA methylation data and microRNA sequencing (miRNA-Seq) data of hepatocellular carcinoma in the cancer genome atlas (TCGA) database[13,14]. Data coordination with TCGA-Assembler was the first step to provide proper data for AI[14]. A similarity network fusion approach predicted cancer subtypes and survival[15]. A gene signature for the metastasis-related recurrence of hepatocellular carcinoma was identified with a classifier model consisting of class prediction algorithms, support vector machine (SVM), nearest centroid, 3-nearest neighbor, 1-nearest neighbor, linear discriminant analysis, and compound covariate prediction, to assess the risk of cancer recurrence in the early stage[16]. Gene mutation sets were identified in liver cancers, including hepatitis-positive samples[17]. SVM learning is useful for classifying and subtyping cancer[18]. Tumor pathology, such as subtyping, grading and staging, can be predicted by deep learning-based AI[19]. Clustering and machine learning methods have been used to classify immunotherapy-responsive triple-negative breast cancer patients[20]. Progressive non-muscle-invasive bladder cancer and muscle-invasive bladder cancer were classified based on the molecular subtype of immunotherapy responsiveness[21]. An interesting classifier model called cancer of unknown primary-AI-Dx predicted the tumor primary site and molecular subtype in RNA profiling[22].

APPLICATION OF AI TECHNOLOGY IN CANCER TREATMENT

Enhanced clinical workflow with AI interventions has been suggested in cancer treatment, which includes AI-guided detection and characterization, AI-guided treatment planning and monitoring, and AI-oriented optimization of the outcome[23]. AI tools can be used in detection of abnormalities, characterization of suspected lesion, and determination of prognosis or response to the treatment[23]. AI technology provides robust tumor descriptors in segmentation, diagnosis, staging and imaging genomics[23]. Radiomic feature extraction from CT images of lung cancer patients was successful to show association with gene expression and prognostic performance[24]. CT-based radiomic features may predict distant metastasis for lung adenocarcinoma patients[25]. The approach in evaluation and validation of novel biomarkers incorporates modified criteria in image data into Response Evaluation Criteria in Solid Tumours in cancer therapy[26]. The results of clinical study in metastatic non-small- cell lung cancer demonstrated that the treatment of pembrolizumab in combination with chemotherapy showed longer overall survival and progression-free survival than chemotherapy alone in the patients without epidermal growth factor receptor or

anaplastic lymphoma kinase mutations[27]. The AI application in medical fields such as early detection, diagnosis, and treatment of diseases is expanding[28]. Clinical data is processed with natural language processing and machine learning of AI, which would be important components in clinical decision making on treatment strategy[28,29] (Figure 1, Table 1).

CONCLUSION

The utilization of AI for cancer recognition is rapidly increasing. The traditional approach may evolve with AI neural networks to create a future field for the planet. The recognition of image data, as well as translated and untranslated transcripts of genes in cancer, will deepen the AI universe.

Table 1 Artificial intelligence application in cancer recognition and treatment

Step	AI application	Recognition/treatment
Early	Natural language processing	Clinical data in human language are translated into AI language to allow AI to recognize cancer
Middle	Machine learning	AI learns the feature of the data to generate the recognition model
Late	Deep learning	AI modeling is further evaluated and modified. Human interprets the results of the AI modeling prediction and decides the clinical treatment strategy

AI: Artificial intelligence.

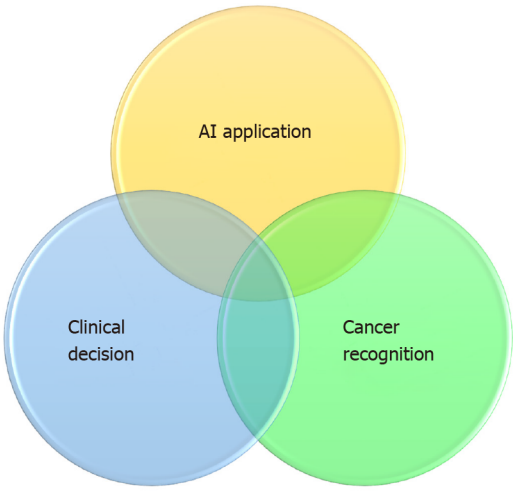

Figure 1 Artificial intelligence application and cancer recognition in clinic. Artificial intelligence is utilized for cancer recognition, which contributes in clinical decision such as the treatment strategy. AI: Artificial intelligence.

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REFERENCES

1 **Bibi N**, Sikandar M, Ud Din I, Almogren A, Ali S. IoMT-Based Automated Detection and Classification of Leukemia Using Deep Learning. *J Healthc Eng* 2020; **2020**: 6648574 [PMID: 33343851 DOI: 10.1155/2020/6648574]
2 **Rajagopalan K**, Babu S. The detection of lung cancer using massive artificial neural network based on soft tissue technique. *BMC Med Inform Decis Mak* 2020; **20**: 282 [PMID: 33129343 DOI: 10.1186/s12911-020-01220-z]
3 **Bang CS**, Lee JJ, Baik GH. Artificial Intelligence for the Prediction of Helicobacter Pylori Infection in Endoscopic Images: Systematic Review and Meta-Analysis Of Diagnostic Test Accuracy. *J Med Internet Res* 2020; **22**: e21983 [PMID: 32936088 DOI: 10.2196/21983]
4 **Zheng L**, Zhang X, Hu J, Gao Y, Zhang M, Li S, Zhou X, Niu T, Lu Y, Wang D. Establishment and Applicability of a Diagnostic System for Advanced Gastric Cancer T Staging Based on a Faster Region-Based Convolutional Neural Network. *Front Oncol* 2020; **10**: 1238 [PMID: 32850373 DOI: 10.3389/fonc.2020.01238]
5 **Brunelli M**, Beccari S, Colombari R, Gobbo S, Giobelli L, Pellegrini A, Chilosi M, Lunardi M, Martignoni G, Scarpa A, Eccher A. iPathology cockpit diagnostic station: validation according to College of American Pathologists Pathology and Laboratory Quality Center recommendation at the Hospital Trust and University of Verona. *Diagn Pathol* 2014; **9** Suppl 1: S12 [PMID: 25565219 DOI: 10.1186/1746-1596-9-S1-S12]
6 **Eccher A**, Neil D, Ciangherotti A, Cima L, Boschiero L, Martignoni G, Ghimenton C, Chilosi M, Giobelli L, Zampicinini L, Casartelli M, Brunelli M. Digital reporting of whole-slide images is safe and suitable for assessing organ quality in preimplantation renal biopsies. *Hum Pathol* 2016; **47**: 115-120 [PMID: 26547252 DOI: 10.1016/j.humpath.2015.09.012]
7 **Girolami I**, Marletta S, Pantanowitz L, Torresani E, Ghimenton C, Barbareschi M, Scarpa A, Brunelli M, Barresi V, Trimboli P, Eccher A. Impact of image analysis and artificial intelligence in thyroid

pathology, with particular reference to cytological aspects. *Cytopathology* 2020; **31**: 432-444 [PMID: 32248583 DOI: 10.1111/cyt.12828]

8 **Govind D**, Jen KY, Matsukuma K, Gao G, Olson KA, Gui D, Wilding GE, Border SP, Sarder P. Improving the accuracy of gastrointestinal neuroendocrine tumor grading with deep learning. *Sci Rep* 2020; **10**: 11064 [PMID: 32632119 DOI: 10.1038/s41598-020-67880-z]

9 **Tanabe S**. How can artificial intelligence and humans work together to fight against cancer? *Artif Intell Cancer* 2020; **1**: 45-50 [DOI: 10.35713/aic.v1.i3.45]

10 **Lee J**, Yoon W, Kim S, Kim D, So CH, Kang J. BioBERT: a pre-trained biomedical language representation model for biomedical text mining. *Bioinformatics* 2020; **36**: 1234-1240 [PMID: 31501885 DOI: 10.1093/bioinformatics/btz682]

11 **Goodfellow IJ**, Pouget-Abadie J, Mirza M, Xu B, Warde-Farley D, Ozair S, Courville A, Bengio Y. Generative adversarial nets. In: Ghahramani Z, Welling M, Cortes C, Lawrence ND, Weinberger KQ, editors. Proceedings of the 27th International Conference on Neural Information Processing Systems - Volume 2; 2014 Dec 8-13; Montreal, Canada. Cambridge: MIT Press, 2014: 2672-2680

12 **Vaswani A**, Shazeer N, Parmar N, Uszkoreit J, Jones L, Gomez AN, Kaiser L, Polosukhin I. Attention is all you need. In: von Luxburg U, Guyon I, Bengio S, Wallach H, Fergus R, editors. Proceedings of the 31st International Conference on Neural Information Processing Systems; 2017 Dec 4-9; Long Beach, United States. New York: Curran Associates Inc., 2017: 6000-6010

13 **Chaudhary K**, Poirion OB, Lu L, Garmire LX. Deep Learning-Based Multi-Omics Integration Robustly Predicts Survival in Liver Cancer. *Clin Cancer Res* 2018; **24**: 1248-1259 [PMID: 28982688 DOI: 10.1158/1078-0432.CCR-17-0853]

14 **Zhu Y**, Qiu P, Ji Y. TCGA-assembler: open-source software for retrieving and processing TCGA data. *Nat Methods* 2014; **11**: 599-600 [PMID: 24874569 DOI: 10.1038/nmeth.2956]

15 **Wang B**, Mezlini AM, Demir F, Fiume M, Tu Z, Brudno M, Haibe-Kains B, Goldenberg A. Similarity network fusion for aggregating data types on a genomic scale. *Nat Methods* 2014; **11**: 333-337 [PMID: 24464287 DOI: 10.1038/nmeth.2810]

16 **Roessler S**, Jia HL, Budhu A, Forgues M, Ye QH, Lee JS, Thorgeirsson SS, Sun Z, Tang ZY, Qin LX, Wang XW. A unique metastasis gene signature enables prediction of tumor relapse in early-stage hepatocellular carcinoma patients. *Cancer Res* 2010; **70**: 10202-10212 [PMID: 21159642 DOI: 10.1158/0008-5472.CAN-10-2607]

17 **Fujimoto A**, Furuta M, Totoki Y, Tsunoda T, Kato M, Shiraishi Y, Tanaka H, Taniguchi H, Kawakami Y, Ueno M, Gotoh K, Ariizumi S, Wardell CP, Hayami S, Nakamura T, Aikata H, Arihiro K, Boroevich KA, Abe T, Nakano K, Maejima K, Sasaki-Oku A, Ohsawa A, Shibuya T, Nakamura H, Hama N, Hosoda F, Arai Y, Ohashi S, Urushidate T, Nagae G, Yamamoto S, Ueda H, Tatsuno K, Ojima H, Hiraoka N, Okusaka T, Kubo M, Marubashi S, Yamada T, Hirano S, Yamamoto M, Ohdan H, Shimada K, Ishikawa O, Yamaue H, Chayama K, Miyano S, Aburatani H, Shibata T, Nakagawa H. Whole-genome mutational landscape and characterization of noncoding and structural mutations in liver cancer. *Nat Genet* 2016; **48**: 500-509 [PMID: 27064257 DOI: 10.1038/ng.3547]

18 **Huang S**, Cai N, Pacheco PP, Narrandes S, Wang Y, Xu W. Applications of Support Vector Machine (SVM) Learning in Cancer Genomics. *Cancer Genomics Proteomics* 2018; **15**: 41-51 [PMID: 29275361 DOI: 10.21873/cgp.20063]

19 **Jiang Y**, Yang M, Wang S, Li X, Sun Y. Emerging role of deep learning-based artificial intelligence in tumor pathology. *Cancer Commun (Lond)* 2020; **40**: 154-166 [PMID: 32277744 DOI: 10.1002/cac2.12012]

20 **He Y**, Jiang Z, Chen C, Wang X. Classification of triple-negative breast cancers based on Immunogenomic profiling. *J Exp Clin Cancer Res* 2018; **37**: 327 [PMID: 30594216 DOI: 10.1186/s13046-018-1002-1]

21 **Song BN**, Kim SK, Mun JY, Choi YD, Leem SH, Chu IS. Identification of an immunotherapy-responsive molecular subtype of bladder cancer. *EBioMedicine* 2019; **50**: 238-245 [PMID: 31735557 DOI: 10.1016/j.ebiom.2019.10.058]

22 **Zhao Y**, Pan Z, Namburi S, Pattison A, Posner A, Balachander S, Paisie CA, Reddi HV, Rueter J, Gill AJ, Fox S, Raghav KPS, Flynn WF, Tothill RW, Li S, Karuturi RKM, George J. CUP-AI-Dx: A tool for inferring cancer tissue of origin and molecular subtype using RNA gene-expression data and artificial intelligence. *EBioMedicine* 2020; **61**: 103030 [PMID: 33039710 DOI: 10.1016/j.ebiom.2020.103030]

23 **Bi WL**, Hosny A, Schabath MB, Giger ML, Birkbak NJ, Mehrtash A, Allison T, Arnaout O, Abbosh C, Dunn IF, Mak RH, Tamimi RM, Tempany CM, Swanton C, Hoffmann U, Schwartz LH, Gillies RJ, Huang RY, Aerts HJWL. Artificial intelligence in cancer imaging: Clinical challenges and applications. *CA Cancer J Clin* 2019; **69**: 127-157 [PMID: 30720861 DOI: 10.3322/caac.21552]

24 **Aerts HJ**, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Carvalho S, Bussink J, Monshouwer R, Haibe-Kains B, Rietveld D, Hoebers F, Rietbergen MM, Leemans CR, Dekker A, Quackenbush J, Gillies RJ, Lambin P. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun* 2014; **5**: 4006 [PMID: 24892406 DOI: 10.1038/ncomms5006]

25 **Coroller TP**, Grossmann P, Hou Y, Rios Velazquez E, Leijenaar RT, Hermann G, Lambin P, Haibe-Kains B, Mak RH, Aerts HJ. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiother Oncol* 2015; **114**: 345-350 [PMID: 25746350 DOI: 10.1016/j.radonc.2015.02.015]

26 **Schwartz LH**, Seymour L, Litière S, Ford R, Gwyther S, Mandrekar S, Shankar L, Bogaerts J, Chen

A, Dancey J, Hayes W, Hodi FS, Hoekstra OS, Huang EP, Lin N, Liu Y, Therasse P, Wolchok JD, de Vries E. RECIST 1.1 - Standardisation and disease-specific adaptations: Perspectives from the RECIST Working Group. *Eur J Cancer* 2016; **62**: 138-145 [PMID: 27237360 DOI: 10.1016/j.ejca.2016.03.082]

27 **Gandhi L**, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* 2018; **378**: 2078-2092 [PMID: 29658856 DOI: 10.1056/NEJMoa1801005]

28 **Jiang F**, Jiang Y, Zhi H, Dong Y, Li H, Ma S, Wang Y, Dong Q, Shen H. Artificial intelligence in healthcare: past, present and future. *Stroke Vasc Neurol* 2017; **2**: 230-243 [PMID: 29507784 DOI: 10.1136/svn-2017-000101]

29 **Komorowski M**, Celi LA, Badawi O, Gordon AC, Faisal AA. The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. *Nat Med* 2018; **24**: 1716-1720 [PMID: 30349085 DOI: 10.1038/s41591-018-0213-5]

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EDITORIAL

Artificial intelligence and colorectal cancer: How far can you go?

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Abstract

Artificial intelligence is an emerging technology whose application is rapidly increasing in several medical fields. The numerous applications of artificial intelligence in gastroenterology have shown promising results, especially in the setting of gastrointestinal oncology. Therefore, we would like to highlight and summarize the research progress and clinical application value of artificial intelligence in the diagnosis, treatment, and prognosis of colorectal cancer to provide evidence for its use as a promising diagnostic and therapeutic tool in this setting.

Key Words: Artificial intelligence; Colorectal cancer; Diagnosis; Treatment; Prognosis

Core Tip: In this editorial, we would like to highlight and summarize the research progress and clinical application value of artificial intelligence in the diagnosis, treatment, and prognosis of colorectal cancer to provide evidence for its use as a promising diagnostic and therapeutic tool in this setting.

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INTRODUCTION

Colorectal cancer (CRC) is a major healthcare concern worldwide. It is the third most common cancer in males, the second most common cancer in females and the fourth leading cause of cancer death worldwide[1-3]. Furthermore, up to 60%-70% of recognized cases in symptomatic patients are diagnosed at an advanced stage[4-6].

Artificial intelligence (AI) is a form of machine technology in which intelligent agents perform functions associated with the human mind, such as learning and problem solving[7-9]; AI algorithms are primarily used for disease diagnosis, treatment and prognosis[10,11].

In the setting of endoscopic diagnosis, AI has been primarily evaluated in 3 clinical scenarios: Polyp detection, polyp characterization (adenomatous *vs* nonadenomatous), and the prediction of invasive cancer within a polypoid lesion[12].

With regard to polyp detection, the adenoma detection rate (ADR), defined as the proportion of patients with at least one colorectal adenoma detected at the first screening colonoscopy among all the patients examined by an endoscopist, represents a pivotal quality measure for colonoscopy[6,13]. In fact, it has been reported that a 1% increase in the ADR is associated with a 3% decrease in interval CRC incidence[6,14,15].

The outcomes reported by different mono- and multicenter randomized clinical trials are highly promising; the overall ADR of these studies was significantly higher when computer-aided diagnosis (CAD) systems were incorporated (up to 80%)[16-20].

With regard to polyp characterization, CAD systems can achieve thresholds of preservation and incorporate valuable endoscopic innovations for diminutive, nonneoplastic rectosigmoid polyps according to various studies[6,21-25].

With regard to differentiation between invasive cancer and nonmalignant adenomatous polyps, an accuracy of 94.1% and 81,2%, respectively, was achieved in two recent studies[26,27].

AI has also been evaluated in the classification and diagnosis of biopsy samples. In a recent systematic review performed by Thakur and coworkers, the authors concluded that artificial intelligence showed promising results in terms of accuracy in diagnosing CRC with regard to tumor classification, tumor microenvironment analysis, and prognosis prediction. However, the scale and quality of the training and validation datasets of most of these studies are insufficiently adequate, limiting the applicability of this technique in clinical practice[28].

With regard to surgical approaches, robot-assisted colorectal surgery has shown better performance than human-alone surgery, in terms of short- and long-term outcomes[10,29].

Additionally, with regard to the pharmacological approach, some studies evaluated targeted drug delivery[30], drug pharmacokinetics[31] and prediction of the rate of drug toxicity[32].

Furthermore, the personalization and precision of cancer treatments have become major themes in oncology research. For example, "Watson for Oncology" is an AI system that can assist in the precision medicine-based treatment of tumors[10,33]. It can automatically extract medical language from doctors' records and translate them into a practical language for learning[10]. This model can be used to identify new cancer sub-populations, analyze their genetic biomarkers, and find effective drug combinations[10].

Finally, the emergence of AI has allowed clinicians to predict the prognoses of CRC patients more easily and precisely by using several approaches. For example, in one study, genetic markers of CRC were used to train a model based on different algorithms[34]. In another study, a computer-aided analysis method for tissue sections based on multifractal analyses of cytokeratin-stained tumor sections was proposed to evaluate the complexity of tumor-stroma interfaces[35]. Other studies have evaluated cytokeratin immunohistochemical images to predict lymph node metastasis[36,37] and the infiltration of immune cells in influencing CRC prognosis[38].

In the near future, AI technology will help doctors diagnose and treat their patients and provide CRC patients with personalized and accurate prognosis evaluations.

CONCLUSION

In conclusion. AI could play a pivotal role in gastrointestinal oncology, especially in the setting of CRC, for tailoring patient treatments and predicting their clinical outcomes[9].

Table 1 Application of artificial intelligence in colorectal cancer

Setting	Application	Ref.
Diagnosis	Polyp identification	[16-20]
	Polyp characterization	[21-25]
	Prediction of invasive cancer within a polypoid lesion	[26,27]
	Search for new diagnostic biomarkers	[10]
	Pathologic biopsy	[28]
Treatment	Preoperative evaluation	[10]
	Robot-assisted surgery	[29]
	Drug delivering in a targeted manner	[30]
	Evaluation of drugs pharmacokinetic	[31]
	Prediction of the rate of toxicity	[32]
	Watson for Oncology project	[33]
Prognosis	Search for new prognostic biomarkers	[38]
	Evaluation of tumour-stroma ratio	[35]
	Prediction of lymph-node metastasis	[36,37]

Future randomized studies could directly increase the overall value (quality and costs) of AI by examining its effects not only in diagnosis (by evaluating colonoscopy findings, endoscopy durations, polyps and ADRs) but also in prognosis and therapy.

Since AI science continues to grow and evolve, the current limitations must be considered as a future challenge; these limitations are also inherited by the medicine applications of AI, including the difficult predictability of situations characterized by some degree of uncertainty[6]. Table 1 shows the applications of AI in CRC.

Future applications of AI could be implemented in all the settings of CRC management, such as the determination of the potential role of noncoding RNAs in tumor diagnosis and treatment[10].

Finally, the integration of AI in human-based medicine has to considered. AI has never been nor will ever be considered a substitute for the physician; on the contrary, it seems to be an extremely helpful tool to be used by the physician who, given his or her ability and skills, is the only one able to process and interpret all the information extracted by the AI to make decisions on patient management.

REFERENCES

1 **Global Burden of Disease Cancer Collaboration**, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park EK, Catalá-López F, deVeber G, Gotay C, Khan G, Hosgood HD 3rd, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrime MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad SM, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Orjuela C, van Gool CH, Violante F, Oh IH, Deribe K, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillmann T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M. The Global Burden of Cancer 2013. *JAMA Oncol* 2015; **1**: 505-527 [PMID: 26181261 DOI: 10.1001/jamaoncol.2015.0735]

2 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

3 **Maida M**, Morreale G, Sinagra E, Ianiro G, Margherita V, Cirrone Cipolla A, Camilleri S. Quality measures improving endoscopic screening of colorectal cancer: a review of the literature. *Expert Rev Anticancer Ther* 2019; **19**: 223-235 [PMID: 30614284 DOI: 10.1080/14737140.2019.1565999]

4 **Mandel JS**, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365-1371 [PMID: 8474513 DOI: 10.1056/NEJM199305133281901]

5 **Maida M**, Macaluso FS, Ianiro G, Mangiola F, Sinagra E, Hold G, Maida C, Cammarota G, Gasbarrini A, Scarpulla G. Screening of colorectal cancer: present and future. *Expert Rev Anticancer Ther* 2017; **17**: 1131-1146 [PMID: 29022408 DOI: 10.1080/14737140.2017.1392243]

6 **Sinagra E**, Badalamenti M, Maida M, Spadaccini M, Maselli R, Rossi F, Conoscenti G, Raimondo D, Pallio S, Repici A, Anderloni A. Use of artificial intelligence in improving adenoma detection rate during colonoscopy: Might both endoscopists and pathologists be further helped. *World J Gastroenterol* 2020; **26**: 5911-5918 [PMID: 33132644 DOI: 10.3748/wjg.v26.i39.5911]

7 **Russell S**, Norvig P. Artificial Intelligence: A Modern Approach, Global Edition. 3rd editon. London: Pearson, 2016

8 **Colom R**, Karama S, Jung RE, Haier RJ. Human intelligence and brain networks. *Dialogues Clin Neurosci* 2010; **12**: 489-501 [PMID: 21319494 DOI: 10.31887/DCNS.2010.12.4/rcolom]

9 **Morreale GC**, Sinagra E, Vitello A, Shahini E, Maida M. Emerging artificial intelligence applications in gastroenterology: A review of the literature. *Artif Intell Gastrointest Endosc* 2020; **1**: 6-18 [DOI: 10.37126/aige.v1.i1.6]

10 **Wang Y**, He X, Nie H, Zhou J, Cao P, Ou C. Application of artificial intelligence to the diagnosis and therapy of colorectal cancer. *Am J Cancer Res* 2020; **10**: 3575-3598 [PMID: 33042269 DOI: 10.7150/thno.49168]

11 **Hamet P**, Tremblay J. Artificial intelligence in medicine. *Metabolism* 2017; **69S**: S36-S40 [PMID: 28126242 DOI: 10.1016/j.metabol.2017.01.011]

12 **Pannala R**, Krishnan K, Melson J, Parsi MA, Schulman AR, Sullivan S, Trikudanathan G, Trindade AJ, Watson RR, Maple JT, Lichtenstein DR. Artificial intelligence in gastrointestinal endoscopy. *VideoGIE* 2020; **5**: 598-613 [PMID: 33319126 DOI: 10.1016/j.vgie.2020.08.013]

13 **Zhao S**, Wang S, Pan P, Xia T, Chang X, Yang X, Guo L, Meng Q, Yang F, Qian W, Xu Z, Wang Y, Wang Z, Gu L, Wang R, Jia F, Yao J, Li Z, Bai Y. Magnitude, Risk Factors, and Factors Associated With Adenoma Miss Rate of Tandem Colonoscopy: A Systematic Review and Meta-analysis. *Gastroenterology* 2019; **156**: 1661-1674. e11 [PMID: 30738046 DOI: 10.1053/j.gastro.2019.01.260]

14 **Rex DK**, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 1997; **112**: 24-28 [PMID: 8978338 DOI: 10.1016/s0016-5085(97)70214-2]

15 **Corley DA**, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**: 1298-1306 [PMID: 24693890 DOI: 10.1056/NEJMoa1309086]

16 **Repici A**, Badalamenti M, Maselli R, Correale L, Radaelli F, Rondonotti E, Ferrara E, Spadaccini M, Alkandari A, Fugazza A, Anderloni A, Galtieri PA, Pellegatta G, Carrara S, Di Leo M, Craviotto V, Lamonaca L, Lorenzetti R, Andrealli A, Antonelli G, Wallace M, Sharma P, Rosch T, Hassan C. Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial. *Gastroenterology* 2020; **159**: 512-520. e7 [PMID: 32371116 DOI: 10.1053/j.gastro.2020.04.062]

17 **Wang P**, Berzin TM, Glissen Brown JR, Bharadwaj S, Becq A, Xiao X, Liu P, Li L, Song Y, Zhang D, Li Y, Xu G, Tu M, Liu X. Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. *Gut* 2019; **68**: 1813-1819 [PMID: 30814121 DOI: 10.1136/gutjnl-2018-317500]

18 **Wang P**, Liu X, Berzin TM, Glissen Brown JR, Liu P, Zhou C, Lei L, Li L, Guo Z, Lei S, Xiong F, Wang H, Song Y, Pan Y, Zhou G. Effect of a deep-learning computer-aided detection system on adenoma detection during colonoscopy (CADe-DB trial): a double-blind randomised study. *Lancet Gastroenterol Hepatol* 2020; **5**: 343-351 [PMID: 31981517 DOI: 10.1016/S2468-1253(19)30411-X]

19 **Gong D**, Wu L, Zhang J, Mu G, Shen L, Liu J, Wang Z, Zhou W, An P, Huang X, Jiang X, Li Y, Wan X, Hu S, Chen Y, Hu X, Xu Y, Zhu X, Li S, Yao L, He X, Chen D, Huang L, Wei X, Wang X, Yu H. Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomised controlled study. *Lancet Gastroenterol Hepatol* 2020; **5**: 352-361 [PMID: 31981518 DOI: 10.1016/S2468-1253(19)30413-3]

20 **Liu WN**, Zhang YY, Bian XQ, Wang LJ, Yang Q, Zhang XD, Huang J. Study on detection rate of polyps and adenomas in artificial-intelligence-aided colonoscopy. *Saudi J Gastroenterol* 2020; **26**: 13-19 [PMID: 31898644 DOI: 10.4103/sjg.SJG_377_19]

21 **Aihara H**, Saito S, Inomata H, Ide D, Tamai N, Ohya TR, Kato T, Amitani S, Tajiri H. Computer-aided diagnosis of neoplastic colorectal lesions using 'real-time' numerical color analysis during autofluorescence endoscopy. *Eur J Gastroenterol Hepatol* 2013; **25**: 488-494 [PMID: 23249604 DOI: 10.1097/MEG.0b013e32835c6d9a]

22 **Kuiper T**, Alderlieste YA, Tytgat KM, Vlug MS, Nabuurs JA, Bastiaansen BA, Löwenberg M, Fockens P, Dekker E. Automatic optical diagnosis of small colorectal lesions by laser-induced autofluorescence. *Endoscopy* 2015; **47**: 56-62 [PMID: 25264763 DOI: 10.1055/s-0034-1378112]

23 **Rath T**, Tontini GE, Vieth M, Nägel A, Neurath MF, Neumann H. In vivo real-time assessment of

colorectal polyp histology using an optical biopsy forceps system based on laser-induced fluorescence spectroscopy. *Endoscopy* 2016; **48**: 557-562 [PMID: 27009081 DOI: 10.1055/s-0042-102251]

24 **Kominami Y**, Yoshida S, Tanaka S, Sanomura Y, Hirakawa T, Raytchev B, Tamaki T, Koide T, Kaneda K, Chayama K. Computer-aided diagnosis of colorectal polyp histology by using a real-time image recognition system and narrow-band imaging magnifying colonoscopy. *Gastrointest Endosc* 2016; **83**: 643-649 [PMID: 26264431 DOI: 10.1016/j.gie.2015.08.004]

25 **Mori Y**, Kudo SE, Misawa M, Saito Y, Ikematsu H, Hotta K, Ohtsuka K, Urushibara F, Kataoka S, Ogawa Y, Maeda Y, Takeda K, Nakamura H, Ichimasa K, Kudo T, Hayashi T, Wakamura K, Ishida F, Inoue H, Itoh H, Oda M, Mori K. Real-Time Use of Artificial Intelligence in Identification of Diminutive Polyps During Colonoscopy: A Prospective Study. *Ann Intern Med* 2018; **169**: 357-366 [PMID: 30105375 DOI: 10.7326/M18-0249]

26 **Takeda K**, Kudo SE, Mori Y, Misawa M, Kudo T, Wakamura K, Katagiri A, Baba T, Hidaka E, Ishida F, Inoue H, Oda M, Mori K. Accuracy of diagnosing invasive colorectal cancer using computer-aided endocytoscopy. *Endoscopy* 2017; **49**: 798-802 [PMID: 28472832 DOI: 10.1055/s-0043-105486]

27 **Ito N**, Kawahira H, Nakashima H, Uesato M, Miyauchi H, Matsubara H. Endoscopic Diagnostic Support System for cT1b Colorectal Cancer Using Deep Learning. *Oncology* 2019; **96**: 44-50 [PMID: 30130758 DOI: 10.1159/000491636]

28 **Thakur N**, Yoon H, Chong Y. Current Trends of Artificial Intelligence for Colorectal Cancer Pathology Image Analysis: A Systematic Review. *Cancers (Basel)* 2020; **12** [PMID: 32668721 DOI: 10.3390/cancers12071884]

29 **Yoon SN**, Kim KY, Kim JW, Lee SC, Kwon YJ, Cho JW, Jung SY, Kim BC. Comparison of short- and long-term outcomes of an early experience with robotic and laparoscopic-assisted resection for rectal cancer. *Hepatogastroenterology* 2015; **62**: 34-39 [PMID: 25911863]

30 **Felfoul O**, Mohammadi M, Taherkhani S, de Lanauze D, Zhong Xu Y, Loghin D, Essa S, Jancik S, Houle D, Lafleur M, Gaboury L, Tabrizian M, Kaou N, Atkin M, Vuong T, Batist G, Beauchemin N, Radzioch D, Martel S. Magneto-aerotactic bacteria deliver drug-containing nanoliposomes to tumour hypoxic regions. *Nat Nanotechnol* 2016; **11**: 941-947 [PMID: 27525475 DOI: 10.1038/nnano.2016.137]

31 **Cruz S**, Gomes SE, Borralho PM, Rodrigues CMP, Gaudêncio SP, Pereira F. In Silico HCT116 Human Colon Cancer Cell-Based Models En Route to the Discovery of Lead-Like Anticancer Drugs. *Biomolecules* 2018; **8** [PMID: 30018273 DOI: 10.3390/biom8030056]

32 **Oyaga-Iriarte E**, Insausti A, Sayar O, Aldaz A. Prediction of irinotecan toxicity in metastatic colorectal cancer patients based on machine learning models with pharmacokinetic parameters. *J Pharmacol Sci* 2019; **140**: 20-25 [PMID: 31105026 DOI: 10.1016/j.jphs.2019.03.004]

33 **Schmidt C**. M. D. Anderson Breaks With IBM Watson, Raising Questions About Artificial Intelligence in Oncology. *J Natl Cancer Inst* 2017; **109** [PMID: 30053147 DOI: 10.1093/jnci/djx113]

34 **Gründner J**, Prokosch HU, Stürzl M, Croner R, Christoph J, Toddenroth D. Predicting Clinical Outcomes in Colorectal Cancer Using Machine Learning. *Stud Health Technol Inform* 2018; **247**: 101-105 [PMID: 29677931]

35 **Mezheyeuski A**, Hrynchyk I, Karlberg M, Portyanko A, Egevad L, Ragnhammar P, Edler D, Glimelius B, Östman A. Image analysis-derived metrics of histomorphological complexity predicts prognosis and treatment response in stage II-III colon cancer. *Sci Rep* 2016; **6**: 36149 [PMID: 27805003 DOI: 10.1038/srep36149]

36 **Zhou YP**, Li S, Zhang XX, Zhang ZD, Gao YX, Ding L, Lu Y. [High definition MRI rectal lymph node aided diagnostic system based on deep neural network]. *Zhonghua Wai Ke Za Zhi* 2019; **57**: 108-113 [PMID: 30704213 DOI: 10.3760/cma.j.issn.0529-5815.2019.02.007]

37 **Lu Y**, Yu Q, Gao Y, Zhou Y, Liu G, Dong Q, Ma J, Ding L, Yao H, Zhang Z, Xiao G, An Q, Wang G, Xi J, Yuan W, Lian Y, Zhang D, Zhao C, Yao Q, Liu W, Zhou X, Liu S, Wu Q, Xu W, Zhang J, Wang D, Sun Z, Zhang X, Hu J, Zhang M, Zheng X, Wang L, Zhao J, Yang S. Identification of Metastatic Lymph Nodes in MR Imaging with Faster Region-Based Convolutional Neural Networks. *Cancer Res* 2018; **78**: 5135-5143 [PMID: 30026330 DOI: 10.1158/0008-5472.CAN-18-0494]

38 **Eyraud D**, Granger B, Bardier A, Loncar Y, Gottrand G, Le Naour G, Siksik JM, Vaillant JC, Klatzmann D, Puybasset L, Charlotte F, Augustin J. Immunological environment in colorectal cancer: a computer-aided morphometric study of whole slide digital images derived from tissue microarray. *Pathology* 2018; **50**: 607-612 [PMID: 30166125 DOI: 10.1016/j.pathol.2018.04.006]

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MINIREVIEWS

Advances in the application of artificial intelligence in solid tumor imaging

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Abstract

Early diagnosis and timely treatment are crucial in reducing cancer-related mortality. Artificial intelligence (AI) has greatly relieved clinical workloads and changed the current medical workflows. We searched for recent studies, reports and reviews referring to AI and solid tumors; many reviews have summarized AI applications in the diagnosis and treatment of a single tumor type. We herein systematically review the advances of AI application in multiple solid tumors including esophagus, stomach, intestine, breast, thyroid, prostate, lung, liver, cervix, pancreas and kidney with a specific focus on the continual improvement on model performance in imaging practice.

Key Words: Artificial intelligence; Oncology; Imaging; Model performance

Core Tip: Many reviews have summarized artificial intelligence applications in the diagnosis and treatment of a single tumor type. However, this is the first review to systematically review how artificial intelligence relieves clinical workloads and changes the current medical workflows while maintaining high quality to provide precision medicine in multiple solid tumors. Due to its clear advantage in imaging

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practice, patients will benefit from early diagnosis and appropriate treatment.

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INTRODUCTION

Cancer is currently a worldwide health problem. Early diagnosis and timely treatment are crucial in reducing cancer-related mortality. Medical imaging is a common technique used to guide the clinical diagnosis of solid tumors. Accurate interpretation of imaging data has become an important but difficult task in the diagnosis process.

Artificial intelligence (AI) refers to an information science that researches and develops theories, methods, technologies and application systems used to simulate, expand and extend human intelligence[1]. With the rapid development of machine learning, deep learning and other crucial AI technologies in the field of image processing in recent years, these approaches have made great contributions to disease classification, prognosis prediction and therapy evaluation and can identify patterns that humans cannot recognize[2-4] (Figure 1). Here, we review the advantage of AI applications in imaging examinations of multiple solid tumors and highlight its great benefits in optimizing the clinical work process, providing accurate tumor assessment for current precision medicine and achieving better diagnosis and treatment results based on its practical data and literature reports.

APPLICATION OF AI IN GASTROINTESTINAL TUMORS

Gastric cancer is one of the most common gastrointestinal malignancies at present, with a poor prognosis and high mortality. Endoscopy and pathological biopsy are still the "gold standard" for the diagnosis of gastric cancer, but they have shortcomings[5]. For example, the sensitivity of endoscopic diagnosis of atrophic gastritis is only 42%, so the rate of missed diagnosis is relatively high[6]. Multipoint biopsy sampling increases the risk of tissue injury and gastrorrhagia[7,8]. Some advanced endoscopic techniques, such as color endoscopy combined with magnification endoscopy and laser confocal microscopy, can provide only images of the mucosal surface of the gastrointestinal tract[7-9]. Billah *et al*[10] used capsule endoscopy along with a convolutional neural network (CNN) and color wavelet features to identify gastrointestinal polyps. Urban *et al*[11] applied deep neural networks to identify colonic polyps from colonoscopy. Lahner *et al*[12] established a decision support system (DSS) for the diagnosis of atrophic gastritis without endoscopy. The diagnostic accuracy of these three protocols was above 96%, which supports the promising generalization of AI-based technologies.

Esophagus squamous cell cancer

Narrow-band imaging (NBI) is an emerging advanced, noninvasive endoscopic technology that can strengthen the evaluation of the surface structure and microvascular morphology of the esophagus and improve the accuracy rate of endoscopic diagnosis[13]. Using NBI to diagnose squamous cell carcinoma can lead to various results due to different judgments from doctors[14,15]. Fukuda *et al*[16] applied a deep CNN model to examine NBI endoscopy video images of squamous cell carcinoma, showing higher detection sensitivity (91.1%) than experts and high detection accuracy (88.3%). Those authors suggested that the AI system can discover tumors > 30 mm or with muscularis mucosa invasion that were missed diagnosis by experts. Compared to endoscopic experts, AI has a better diagnostic performance.

Atrophied gastritis

The CNN-chronic atrophic gastritis approach developed by Zhang *et al*[7] has a good

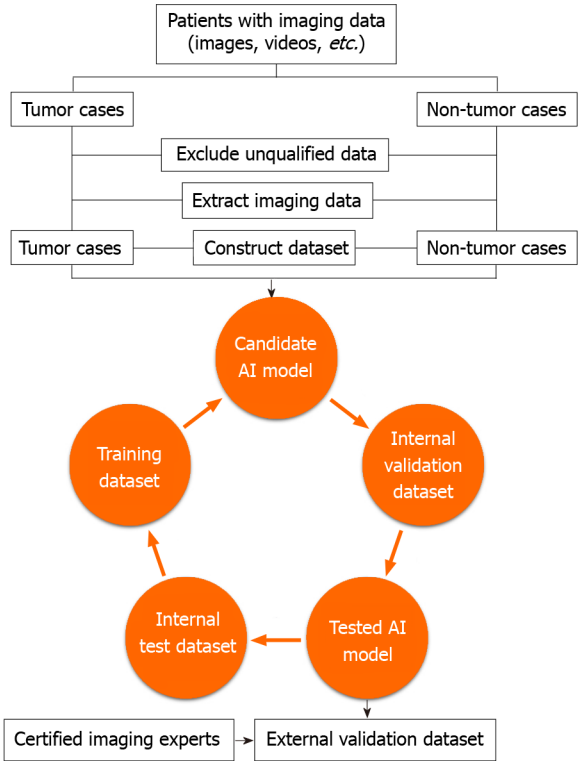

Figure 1 A flowchart of artificial intelligence model construction. AI: Artificial intelligence.

classification performance for recognizing chronic atrophic gastritis based on gastric antrum images whose area under the curve (AUC) was close to 0.99. The accuracy, sensitivity and specificity of CNN-chronic atrophic gastritis in the field of atrophic gastritis diagnosis are all above 0.94. In this study, 1458 mild cases, 1348 moderate cases and 38 severe cases of atrophic gastritis were tested by the CNN model, and the accuracy rates were 0.93, 0.95 and 0.99, respectively, indicating good consistency of the CNN model recognition with the clinical diagnosis of atrophic gastritis.

However, the literature has reported that AI technology used for stomach cancer or esophageal stomach adenocarcinoma is susceptible to problems related to tumor morphology, atrophic change, uneven mucosal background, *etc.*, which leads to low specificity and high false positive rate (FPR)[17]. Several studies indicated that the application of AI in the clinic has high accuracy. If AI technology is combined with endoscopy doctors, then endoscopy can help doctors better diagnose atrophic gastritis, increase the rate of early gastric cancer diagnosis and avoid unnecessary pathological biopsy[18,19].

Early gastric cancer

Regarding small early gastric tumors, Abe *et al*[18] showed that AI technology can find anomalies faster than endoscopy doctors (45.5 s *vs* 173.0 min), and it also shows higher sensitivity (58.4% *vs* 31.9%). However, the positive predictive value (PPV) and specificity of AI technology were relatively lower than those of endoscopy doctors (26.0% *vs* 46.2% and 87.3% *vs* 97.0%, respectively)[18]. A computer-aided design (CAD) system is used in stationary images of magnifying endoscopy combined with NBI, which have an accuracy rate for early gastric cancer diagnosis of 85.3%[20]. When endoscopy cannot identify and capture images of lesions, magnifying endoscopy combined with NBI video in the CAD system can help the real-time clinical diagnosis of early gastric cancer. Horiuchi *et al*[19] proposed that the diagnostic performance of the CAD system using magnifying endoscopy combined with NBI video is equal to or better than that of 11 experienced endoscopic experts in early gastric cancer. The AUC was 0.8684, and its accuracy, sensitivity, specificity, PPV and negative predictive value were 85.1%, 87.4%, 82.8%, 83.5% and 86.7%, respectively[19].

Colorectal cancer

Colorectal colonoscopy is the key technique for the diagnosis of colorectal polyps. However, several studies have shown that 15.4% of colorectal lesions (≤ 3 mm) were

diagnosed as adenomas under endoscopy but were judged as normal mucosa *via* pathological examination[21]. Intraobserver and interobserver discrepancies are the main problem[22]. Therefore, some studies have suggested that using AI techniques combined with endoscopy and imaging may help physicians identify colorectal lesions and perform pathological classification and prognosis prediction[22].

Shahidi *et al*[21] established a real-time AI-based clinical DSS to assess the differences between results from endoscopy and pathology in lesions ≤ 3 mm. Of the 644 lesions, 458 lesions reached agreement, while significant differences were found in 99 cases (adenoma under endoscopy but normal mucosa by pathologic examination). When using the clinical DSS for further evaluation, they found that the clinical DSS data of 90 cases conformed to those from endoscopy (coincidence rate was 90.9%), supporting AI objectivity prior to pathological examination and interpretation[21]. Yang *et al*[22] proposed a CNN model whose diagnosis accuracy was better than or similar to that of endoscopic experts (71.5% *vs* 67.5%), and applications that support the CNN model can help endoscopic physicians identify colorectal lesions to reduce the misdiagnosis rate. The CNN model can also extend the discrimination ability between advanced colorectal cancer and noncancerous lesions, helping endoscopy doctors choose the best treatment strategy effectively[22]. Randomized clinical trials are needed to determine if the CNN model applied to real-time endoscopic video can help endoscopic doctors detect tiny or negligible lesions in the examination.

Wang *et al*[23] explored the feasibility of faster region-based CNN technology. They used transfer learning technology and images and features of the ImageNet VGG16 model to automatically identify the positive circumferential resection margin in high-resolution magnetic resonance imaging (MRI) of rectal cancer, and the accuracy, sensitivity and specificity were 93.2%, 83.8% and 95.6%, respectively[23]. The use of ^{18}F fluorodeoxyglucose-positron emission tomography (PET)/computed tomography (CT) to assess early changes in glucose metabolism parameters during neoadjuvant chemotherapy can predict treatment efficacy[24,25]. Traditional ^{18}F fluorodeoxyglucose-PET/CT cannot accurately and safely select patients for organ preservation strategies[26]. Williams *et al*[27] suggested that random forest is one type of AI technique used for tumor classification and regression evaluation. Shen *et al*[28] used random forest to demonstrate that the radiomics obtained from baseline ^{18}F fluorodeoxyglucose-PET could accurately predict pathological complete response with 95.3% accuracy.

APPLICATION OF AI IN BREAST TUMORS

Ultrasound and radiology are common imaging techniques in breast examination for cancer screening, diagnosis and treatment. Ultrasound is important for the noninvasive measurement of cancer lesions and lymphatic metastasis, increasing the positive diagnostic rate for tiny, aggressive and lymph node-negative breast cancer[29]. However, ultrasound has lower diagnostic specificity and PPV for breast cancer[30]. For example, the axillary positive detection rate of pathological biopsy is 15% to 20%, which is often neglected by ultrasound, especially in those with unspecific characteristics, such as unclear, irregularly shaped edges or fat loss[31]. Although MRI is highly sensitive for the diagnosis of breast cancer, its FPR is as high as 74%[32]. Molybdenum target X-rays are sensitive to microcalcification with the advantage of high cost performance. However, regarding dense breasts where lesions are probably hidden, molybdenum target X-ray has limitations with a lower detection rate[33].

Zhou *et al*[29] proposed a CNN-based deep learning model to predict lymph node metastasis according to the characteristics of primary breast cancer under ultrasound. The data showed that its AUC was approximately 90%, and the sensitivity and specificity were above 80% and 70%, respectively. Mango *et al*[30] integrated their AI-based decision support system into ultrasonic images, and the results showed that this technique is helpful in Breast Imaging Reporting and Data System classification, reducing the intraobserver and interobserver variabilities. The variability incidence of ultrasound only in Breast Imaging Reporting and Data System 3 to Breast Imaging Reporting and Data System 4A or above was 13.6%, and it decreased to 10.8% when ultrasound was combined with decision support.

Spick *et al*[34] showed that adding diffusion-weighted imaging into MRI-guided vacuum-assisted breast biopsy could reduce the FPR by more than 30%. Penco *et al*[32] verified the accuracy of MRI-guided vacuum-assisted breast biopsy in comparison with histopathological results. The results exhibited 94% accuracy, 84% sensitivity and 77% specificity, with a negative predictive value of up to 97%. Adachi *et al*[31] com-

pared the diagnostic performance in dynamic contrast-enhanced magnetic resonance for breast cancer detection of AI using RetinaNet to that of expert readers; the former had a higher diagnostic performance than the latter (AUC 0.925 *vs* 0.884). With the support of AI, the diagnostic performance of expert readers was significantly improved (AUC was 0.899). The sensitivity and specificity of independent AI, experts not using AI and experts using AI in breast cancer diagnosis were 0.926, 0.847, 0.889 and 0.828, 0.841, 0.823, respectively. However, AI may misdiagnose normal breast tissue as malignant due to background parenchymal enhancement or tissue density or misdiagnose invasive ductal carcinoma near the axilla as normal axillary lymph nodes[31].

Sasaki *et al*[35] proposed that AI-based Transpara systems reduced the differences between computers and experts in the detection sensitivity to breast cancer *via* molybdenum targets. The expert detection sensitivity was 89%; with the Transpara system, the detection sensitivity for malignant lesions was increased to 95%[35]. When interpreting breast images, the Transpara system can significantly increase AUC and diagnostic sensitivity without increasing reading time[36].

In summary, AI technology increases the detection sensitivity of latent breast lesions while maintaining higher specificity. This technology also reduces the variability in interpretation and helps to improve the clinical diagnostic performance.

APPLICATION OF AI IN THYROID TUMORS

In recent years, with the increasing incidence rate of thyroid cancer, the accurate classification of thyroid lesions and the prediction of lymph node metastasis have been prioritized to be the core of clinical intervention[37,38]. Ultrasound is a noninvasive, easily accessible and economical examination tool, but its accuracy may vary according to the different professional backgrounds of the readers.

Barczyński *et al*[39] verified that the S-Detect™ model in real-time CAD system had no significant difference from experienced radiologists in sensitivity, accuracy and negative predictive value of thyroid tumor classification. The overall accuracy of disease evaluation was 76% for surgical doctors who had basic ultrasonic skills not using the CAD system but 82% for doctors with experience using the CAD system[39]. The sensitivity and negative predictive value of lesion classification by the CAD system was similar to those by ultrasonic experts. It further helped to locate the thyroid nodules for further puncture cytology. Nevertheless, the S-Detect™ model had defects in identifying calcifications[40].

Postoperative lymph node metastasis is a key factor in the local recurrence of thyroid carcinoma. It is necessary to use CT or ultrasound to judge whether lymph node metastasis is present before surgery[37,38]. A study conducted by Lee *et al*[41] confirmed that the AUC of the CAD system based on deep learning in the classification of thyroid neck lymph node metastasis from preoperative CT images was 0.884, and its diagnostic accuracy, sensitivity, specificity, PPV and negative predictive value were 82.8%, 80.2%, 83.0%, 83.0% and 80.2%, respectively.

APPLICATION OF AI IN PROSTATE CANCER

Serum prostate specific antigen (PSA), digital rectal examination and transrectal prostate ultrasound-guided prostate puncture are the main methods for the early diagnosis of prostate cancer[42]. High-level PSA (> 2 ng/mL) is an important indicator of postoperative monitoring and identifying the recurrence of prostate cancer[43].

Biopsy technology guided by MRI/ultrasound improves the clinical detection of prostate cancer[44,45]. MRI detects pathological changes of Prostate Imaging Reporting and Data System classification is affected by poor intrareader and inter-reader consistency, leading to a 40% difference in targeted biopsy. By adding AI, it will converge Prostate Imaging Reporting and Data System and improve reader consistency, achieving a better (86%) agreement of detected results and pathological diagnosis[46].

Deep learning applications in the field of prostate malignant tumors have been widely used with MRI[47,48]. Although some patients were treated with radical prostate surgery and serum prostate specific antigen < 1, ^{11}C-choline PET/CT still showed a 20.5% positive rate[49]. Prostate uptake of ^{18}F-choline is associated with the overall survival rate, making it as important as serum prostate specific antigen and Gleason scores in identifying high-risk and low-risk patients. Polymeri *et al*[50] used

an automatic estimation method based on deep learning, and the obtained ^{18}F-choline uptake value (71 mL) could reach radiologists' visual estimates (65 mL and 80 mL) within seconds. This approach significantly improved the accuracy and precision of PET/CT imaging in the diagnosis of prostate cancer.

Raciti *et al*[43] used the software Paige Prostate Alpha to significantly increase the detection rate of prostate cancer while maintaining high specificity. Especially for small, poorly differentiated tumors, the sensitivity can be increased to 30% up to 90%. Similar AI systems can also be used to detect micrometastases in prostate cancer.

APPLICATION OF AI IN LUNG CANCER

When using CT to screen pulmonary nodules, lung-Reporting and Data System can increase sensitivity, but its FPR is also high[51]. The CAD method has 100% sensitivity, but its specificity is extremely low (up to 8.2 false positive nodules per scan)[51]. The negative predictive value of PET/CT for lymph node lesions of peripheral T1 tumors (≤ 3 cm) is as high as 92%-94%[52].

Chauvie *et al*[51] attempted to apply new methods to digital tomosynthesis: (1) Binomial visual analysis, PPV (0.14) and sensitivity (0.95); (2) Pulmonary-Reporting and Data System, PPV (0.19) and sensitivity (0.65); (3) Logistic regression, PPV (0.29) and sensitivity (0.20); (4) Random forest, PPV (0.40) and sensitivity (0.30); and (5) Neural network, PPV (0.95) and sensitivity (0.90). These data indicated that the neural network was the only predictor of lung cancer with a high PPV value and no loss in sensitivity. Tau *et al*[52] used CNN to analyze the characteristics of the primary tumor based on PET and to evaluate the existence of lymph node metastasis in newly diagnosed non-small cell lung cancer patients. The sensitivity, specificity and accuracy of predicting positive lymph nodes were 0.74 ± 0.32, 0.84 ± 0.16 and 0.80 ± 0.17, respectively; those of predicting distal metastasis were 0.45 ± 0.08, 0.79 ± 0.06 and 0.63 ± 0.05, respectively. The sensitivity of predicting distant lymph node metastasis was low (24% at prophase and 45% at the end of the monitoring period). CNN had high specificity (91% in the M1 group and 79% in the follow-up group), but the PPV and negative predictive value in class M were lower at the end of follow-up (54.5% and 68.6%).

AI APPLICATION IN OTHER SOLID TUMORS

Hepatocellular carcinoma

The texture analysis of contrast-enhanced magnetic resonance is considered an image tag for predicting the early reaction of hepatocellular carcinoma patients before transarterial chemoembolization (TACE) treatment[53]. Its accuracy for the evaluation of complete remission and incomplete remission was 0.76. Preoperative dynamic CT texture analysis in the prediction of hepatocellular carcinoma response to TACE treatment has certain value. Peng *et al*[54] used a CT-based deep learning technique (transfer learning) that compensated for the inaccuracy of the result caused by insufficient image information. Further studies showed that the three groups (one training set and two validation sets) of data showed a high AUC for predicting the response to TACE treatment: complete response (0.97, 0.98, 0.97), partial response (0.96, 0.96, 0.96), stable condition (0.95, 0.95, 0.94) and disease progression (0.96, 0.94, 0.97); simultaneously, the accuracy reached 84.0%, 85.1% and 82.8%[54]. Therefore, the CT-based deep learning model helps physicians preliminarily estimate the initial response of hepatocellular carcinoma patients to TACE treatment and helps to predict the therapeutic effect of TACE.

Cervical cancer

Colposcopy is widely used in the detection of cervical intraepithelial neoplasia, and it can guide cervical biopsy in women suspected of having cytological abnormalities or human papillomavirus infection[55,56]. In low- and middle-income countries with a lack of tools for colposcopy, the diagnostic accuracy of cervical biopsy to detect cervical intraepithelial neoplasia is quite low (30%-70%)[57]. The development and application of AI-guided (*e.g.*, support vector machine) digital colposcopy helped solve the bottlenecks and improved the screening effectiveness of cervical cancer to better understand the characteristics of cervical lesions[58]. Another advantage of AI is the "real-time" diagnosis report, which continues to optimize clinical workflows[58].

Pancreatic cancer

Accurate segmentation of the pancreas is important to AI training and AI assisted guidance. Wolz *et al*[59] used multi atlas technology, which only achieved a dice similarity coefficient (DSC) of 0.70. Summers *et al*[60] used deep learning technology, which reached a DSC of 0.78%. Wang *et al*[61] proposed that interactive fully convolutional network for the segmentation of the pancreas did not achieve satisfactory results. Boers *et al*[62] assumed that the latest interactive U-Net neural structure is better than interactive fully convolutional network because it can produce a better initial segmentation (DSC 78.1% ± 8.7% *vs* DSC 72.3% ± 11.4%), achieving expert performance faster than artificial division (interactive U-net 8 min to 86% DSC, artificial segmentation 15 min to 87.5% DSC). The average time cost fell 48.4%, but simultaneously due to the low content of visceral fat in some patients, the boundary between the pancreas and surrounding tissues was not clear, which may lead to poor segmentation performance.

Renal cancer

Histopathology is the gold standard for clear cell renal cell carcinoma evaluation[63]. The World Health Organization/International Society of Urological Pathology grading system is used to predict the prognosis of renal clear cell carcinoma[64-66]. Using CT or MRI indications to describe the grading of clear cell renal cell carcinoma is often influenced by subjective factors[67-70]. Cui *et al*[71] studied the machine learning algorithm to extract and analyze the profiles of tiny tumors. Further grading prediction of clear cell renal cell carcinoma by multiparameter MRI or multiphase CT-based machine learning provides a valuable noninvasive assessment for clinicians in the preoperative treatment of renal tumors[71].

CONCLUSION

AI has clear characteristics of high efficiency, specificity and sensitivity in the classification, identification and diagnosis of solid tumor. After its integration into imaging technology, AI optimizes clinical workflows, decreases the discrepancy between the readers and reduces the misdiagnosis rate, which helps clinicians effectively choose appropriate therapeutic strategies and accurately predict the prognosis (Table 1). All these improvements bring great advantages and convenience to current precision medicine. Nevertheless, problems still exist. For example, the FPR increases due to the morphology of the tumors or the uneven mucosal background and the identification failure of calcification because of technical defects. Therefore, AI cannot be a complete replacement of humans in the contemporary situation. We believe that with the continuous improvement of AI technology, the application of AI in tumor diagnosis and treatment will have better prospects in tumors not limited only to solid tumors.

Table 1 Summary of artificial intelligence application in clinical imaging examination

Publish date	Ref.	AI	Application scenarios	Sensitivity	Accuracy	Specificity	PPV	NPV	Detection time	Variation	Volume	AUC	DSC
10/2020	Fukuda *et al*[16]	CNN	Diagnosis of esophagus squamous cell cancer	91.1%	88.3%								
05/2020	Zhang *et al*[7]	CNN	Diagnosis of chronic atrophic gastritis	94.5%	94.2%	94.0%						0.99	
10/2020	Horiuchi *et al*[19]	CAD	Diagnosis of early gastric cancer	87.4%	85.1%	82.8%	83.5%	86.7%				0.8684	
02/2020	Wang *et al*[23]	Faster R-CNN	Circumferential resection margin of rectal cancer	83.8%	93.2%	95.6%							
03/2020	Shen *et al*[28]	RF	Pathological complete response of rectal cancer		95.3%								
01/2021	Abe *et al*[18]	CNN	Diagnosis of gastric cancer	58.4%		87.3%	26.0%		45.5 s				
01/2020	Zhou *et al*[29]	CNN	Lymph node metastasis prediction from primary breast cancer	> 80%		> 70%						0.9	
03/2020	Penco *et al*[32]	DWI	MRI-guided vacuum-assisted breast biopsy	84.0%	94.0%	77.0%		97.0%					
05/2020	Adachi *et al*[31]	RetinaNet	Diagnosis of breast cancer	92.6%		82.8%						0.925	
		Readers without RetinaNet		84.7%		84.1%						0.884	
		Readers with RetinaNet		88.9%		82.3%						0.899	
02/2020	Sasaki *et al*[35]	Experts	Diagnosis of breast cancer	89.0%									
		Experts with Transpara system		95.0%									
06/2020	Mango *et al*[30]	US	Diagnosis of BI-RADS 3 to BI-RADS 4A or above of breast cancer							13.6%			
		US+DS								10.8%			
02/2020	Barczyński *et al*[39]	Doctors without CAD	Classification of thyroid tumor		76.0%								
		Doctors with CAD			82.0%								
06/2020	Lee *et al*[41]	CAD	Diagnosis of thyroid neck lymph node metastasis	80.2%	82.8%	83.0%	83.0%	80.2%				0.884	
03/2020	Polymeri *et al*[50]	CNN	Prostate gland uptake in PET/CT								71 mL		
10/2020	Raciti *et al*[43]	Paige Prostate	Diagnosis of prostate cancer	90.0%									

		Alpha									
07/2020	Chauvie *et al*[51]	Binomial visual analysis	Lung DTS	95.0%			14.0%				
		Pulmonary-RADS		65.0%			19.0%				
		Logistic regression		20.0%			29.0%				
		RF		30.0%			40.0%				
		Neural network		90.0%			95.0%				
07/2020	Tau *et al*[52]	CNN	Diagnosis of lymph node metastasis of lung cancer	74% ± 32%	80% ± 17%	84% ± 16%					
			Predicting of distal metastasis of lung cancer	45% ± 8%	63% ± 5%	79% ± 6%	54.5%	68.6%			
01/2020	Peng *et al*[54]	Transfer learning	Predicting of TACE treatment response of hepatocellular carcinoma		> 82.8%					> 0.94	
09/2013	Wolz *et al*[59]	Multi atlas technology	Segmentation of the pancreas								70.0%
08/2020	Gibson *et al*[62]	Deep learning technology									78.0%
		iFCN									72.3% ± 11.4%
		Artificial segmentation									15 min to 87.5% DSC

AI: Artificial intelligence; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve; DSC: Dice similarity coefficient; CNN: Convolutional neural network; Faster R-CNN: Faster region-based convolutional neural network; RF: Random forest; DWI: Diffusion-weighted imaging; US: Ultrasound; DS: Decision support; CAD: Computer-aided design; DTS: Digital tomosynthesis; TACE: Transarterial chemoembolization; iFCN: Interactive fully convolutional network; BI-RADS: Breast Imaging Reporting and Data System; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography; RADS: Reporting and Data System.

REFERENCES

1 **Zhou B**, Xu JW, Cheng YG, Gao JY, Hu SY, Wang L, Zhan HX. Early detection of pancreatic cancer: Where are we now and where are we going? *Int J Cancer* 2017; **141**: 231-241 [PMID: 28240774 DOI: 10.1002/ijc.30670]

2 **Ding MQ**, Chen L, Cooper GF, Young JD, Lu X. Precision Oncology beyond Targeted Therapy: Combining Omics Data with Machine Learning Matches the Majority of Cancer Cells to Effective Therapeutics. *Mol Cancer Res* 2018; **16**: 269-278 [PMID: 29133589 DOI: 10.1158/1541-7786.MCR-17-0378]

3 **Bibault JE**, Giraud P, Burgun A. Big Data and machine learning in radiation oncology: State of the art and future prospects. *Cancer Lett* 2016; **382**: 110-117 [PMID: 27241666 DOI: 10.1016/j.canlet.2016.05.033]

4 **Fröhlich H**, Balling R, Beerenwinkel N, Kohlbacher O, Kumar S, Lengauer T, Maathuis MH, Moreau Y, Murphy SA, Przytycka TM, Rebhan M, Röst H, Schuppert A, Schwab M, Spang R, Stekhoven D, Sun J, Weber A, Ziemek D, Zupan B. From hype to reality: data science enabling personalized medicine. *BMC Med* 2018; **16**: 150 [PMID: 30145981 DOI: 10.1186/s12916-018-1122-7]

5 **Feng W**, Ding Y, Zong W, Ju S. Non-coding RNAs in regulating gastric cancer metastasis. *Clin Chim Acta* 2019; **496**: 125-133 [PMID: 31276633 DOI: 10.1016/j.cca.2019.07.003]

6 **Du Y**, Bai Y, Xie P, Fang J, Wang X, Hou X, Tian D, Wang C, Liu Y, Sha W, Wang B, Li Y, Zhang

G, Shi R, Xu J, Huang M, Han S, Liu J, Ren X, Wang Z, Cui L, Sheng J, Luo H, Zhao X, Dai N, Nie Y, Zou Y, Xia B, Fan Z, Chen Z, Lin S, Li ZS; Chinese Chronic Gastritis Research group. Chronic gastritis in China: a national multi-center survey. *BMC Gastroenterol* 2014; **14**: 21 [PMID: 24502423 DOI: 10.1186/1471-230X-14-21]

7 **Zhang Y**, Li F, Yuan F, Zhang K, Huo L, Dong Z, Lang Y, Zhang Y, Wang M, Gao Z, Qin Z, Shen L. Diagnosing chronic atrophic gastritis by gastroscopy using artificial intelligence. *Dig Liver Dis* 2020; **52**: 566-572 [PMID: 32061504 DOI: 10.1016/j.dld.2019.12.146]

8 **Guimarães P**, Keller A, Fehlmann T, Lammert F, Casper M. Deep-learning based detection of gastric precancerous conditions. *Gut* 2020; **69**: 4-6 [PMID: 31375599 DOI: 10.1136/gutjnl-2019-319347]

9 **Liu T**, Zheng H, Gong W, Chen C, Jiang B. The accuracy of confocal laser endomicroscopy, narrow band imaging, and chromoendoscopy for the detection of atrophic gastritis. *J Clin Gastroenterol* 2015; **49**: 379-386 [PMID: 25485568 DOI: 10.1097/MCG.0000000000000164]

10 **Billah M**, Waheed S, Rahman MM. An Automatic Gastrointestinal Polyp Detection System in Video Endoscopy Using Fusion of Color Wavelet and Convolutional Neural Network Features. *Int J Biomed Imaging* 2017; **2017**: 9545920 [PMID: 28894460 DOI: 10.1155/2017/9545920]

11 **Urban G**, Tripathi P, Alkayali T, Mittal M, Jalali F, Karnes W, Baldi P. Deep Learning Localizes and Identifies Polyps in Real Time With 96% Accuracy in Screening Colonoscopy. *Gastroenterology* 2018; **155**: 1069-1078. e8 [PMID: 29928897 DOI: 10.1053/j.gastro.2018.06.037]

12 **Lahner E**, Grossi E, Intraligi M, Buscema M, Corleto VD, Delle Fave G, Annibale B. Possible contribution of artificial neural networks and linear discriminant analysis in recognition of patients with suspected atrophic body gastritis. *World J Gastroenterol* 2005; **11**: 5867-5873 [PMID: 16270400 DOI: 10.3748/wjg.v11.i37.5867]

13 **Muto M**, Minashi K, Yano T, Saito Y, Oda I, Nonaka S, Omori T, Sugiura H, Goda K, Kaise M, Inoue H, Ishikawa H, Ochiai A, Shimoda T, Watanabe H, Tajiri H, Saito D. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J Clin Oncol* 2010; **28**: 1566-1572 [PMID: 20177025 DOI: 10.1200/JCO.2009.25.4680]

14 **Ohmori M**, Ishihara R, Aoyama K, Nakagawa K, Iwagami H, Matsuura N, Shichijo S, Yamamoto K, Nagaike K, Nakahara M, Inoue T, Aoi K, Okada H, Tada T. Endoscopic detection and differentiation of esophageal lesions using a deep neural network. *Gastrointest Endosc* 2020; **91**: 301-309. e1 [PMID: 31585124 DOI: 10.1016/j.gie.2019.09.034]

15 **Ishihara R**, Takeuchi Y, Chatani R, Kidu T, Inoue T, Hanaoka N, Yamamoto S, Higashino K, Uedo N, Iishi H, Tatsuta M, Tomita Y, Ishiguro S. Prospective evaluation of narrow-band imaging endoscopy for screening of esophageal squamous mucosal high-grade neoplasia in experienced and less experienced endoscopists. *Dis Esophagus* 2010; **23**: 480-486 [PMID: 20095991 DOI: 10.1111/j.1442-2050.2009.01039.x]

16 **Fukuda H**, Ishihara R, Kato Y, Matsunaga T, Nishida T, Yamada T, Ogiyama H, Horie M, Kinoshita K, Tada T. Comparison of performances of artificial intelligence versus expert endoscopists for real-time assisted diagnosis of esophageal squamous cell carcinoma (with video). *Gastrointest Endosc* 2020; **92**: 848-855 [PMID: 32505685 DOI: 10.1016/j.gie.2020.05.043]

17 **Iwagami H**, Ishihara R, Aoyama K, Fukuda H, Shimamoto Y, Kono M, Nakahira H, Matsuura N, Shichijo S, Kanesaka T, Kanzaki H, Ishii T, Nakatani Y, Tada T. Artificial intelligence for the detection of esophageal and esophagogastric junctional adenocarcinoma. *J Gastroenterol Hepatol* 2021; **36**: 131-136 [PMID: 32511793 DOI: 10.1111/jgh.15136]

18 **Abe S**, Oda I. How can endoscopists adapt and collaborate with artificial intelligence for early gastric cancer detection? *Dig Endosc* 2021; **33**: 98-99 [PMID: 32455500 DOI: 10.1111/den.13751]

19 **Horiuchi Y**, Hirasawa T, Ishizuka N, Tokai Y, Namikawa K, Yoshimizu S, Ishiyama A, Yoshio T, Tsuchida T, Fujisaki J, Tada T. Performance of a computer-aided diagnosis system in diagnosing early gastric cancer using magnifying endoscopy videos with narrow-band imaging (with videos). *Gastrointest Endosc* 2020; **92**: 856-865. e1 [PMID: 32422155 DOI: 10.1016/j.gie.2020.04.079]

20 **Horiuchi Y**, Aoyama K, Tokai Y, Hirasawa T, Yoshimizu S, Ishiyama A, Yoshio T, Tsuchida T, Fujisaki J, Tada T. Convolutional Neural Network for Differentiating Gastric Cancer from Gastritis Using Magnified Endoscopy with Narrow Band Imaging. *Dig Dis Sci* 2020; **65**: 1355-1363 [PMID: 31584138 DOI: 10.1007/s10620-019-05862-6]

21 **Shahidi N**, Rex DK, Kaltenbach T, Rastogi A, Ghalehjegh SH, Byrne MF. Use of Endoscopic Impression, Artificial Intelligence, and Pathologist Interpretation to Resolve Discrepancies Between Endoscopy and Pathology Analyses of Diminutive Colorectal Polyps. *Gastroenterology* 2020; **158**: 783-785. e1 [PMID: 31863741 DOI: 10.1053/j.gastro.2019.10.024]

22 **Yang YJ**, Cho BJ, Lee MJ, Kim JH, Lim H, Bang CS, Jeong HM, Hong JT, Baik GH. Automated Classification of Colorectal Neoplasms in White-Light Colonoscopy Images *via* Deep Learning. *J Clin Med* 2020; **9** [PMID: 32456309 DOI: 10.3390/jcm9051593]

23 **Wang D**, Xu J, Zhang Z, Li S, Zhang X, Zhou Y, Lu Y. Evaluation of Rectal Cancer Circumferential Resection Margin Using Faster Region-Based Convolutional Neural Network in High-Resolution Magnetic Resonance Images. *Dis Colon Rectum* 2020; **63**: 143-151 [PMID: 31842158 DOI: 10.1097/DCR.0000000000001519]

24 **Guillem JG**, Moore HG, Akhurst T, Klimstra DS, Ruo L, Mazumdar M, Minsky BD, Saltz L, Wong WD, Larson S. Sequential preoperative fluorodeoxyglucose-positron emission tomography assessment of response to preoperative chemoradiation: a means for determining longterm outcomes of rectal cancer. *J Am Coll Surg* 2004; **199**: 1-7 [PMID: 15217621 DOI:

10.1016/j.jamcollsurg.2004.02.024]

25 **Capirci C**, Rampin L, Erba PA, Galeotti F, Crepaldi G, Banti E, Gava M, Fanti S, Mariani G, Muzzio PC, Rubello D. Sequential FDG-PET/CT reliably predicts response of locally advanced rectal cancer to neo-adjuvant chemo-radiation therapy. *Eur J Nucl Med Mol Imaging* 2007; **34**: 1583-1593 [PMID: 17503039 DOI: 10.1007/s00259-007-0426-1]

26 **Joye I**, Deroose CM, Vandecaveye V, Haustermans K. The role of diffusion-weighted MRI and (18)F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: a systematic review. *Radiother Oncol* 2014; **113**: 158-165 [PMID: 25483833 DOI: 10.1016/j.radonc.2014.11.026]

27 **Williams JK**. Using random forests to diagnose aviation turbulence. *Mach Learn* 2014; **95**: 51-70 [PMID: 26549933 DOI: 10.1007/s10994-013-5346-7]

28 **Shen WC**, Chen SW, Wu KC, Lee PY, Feng CL, Hsieh TC, Yen KY, Kao CH. Predicting pathological complete response in rectal cancer after chemoradiotherapy with a random forest using ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography radiomics. *Ann Transl Med* 2020; **8**: 207 [PMID: 32309354 DOI: 10.21037/atm.2020.01.107]

29 **Zhou LQ**, Wu XL, Huang SY, Wu GG, Ye HR, Wei Q, Bao LY, Deng YB, Li XR, Cui XW, Dietrich CF. Lymph Node Metastasis Prediction from Primary Breast Cancer US Images Using Deep Learning. *Radiology* 2020; **294**: 19-28 [PMID: 31746687 DOI: 10.1148/radiol.2019190372]

30 **Mango VL**, Sun M, Wynn RT, Ha R. Should We Ignore, Follow, or Biopsy? *AJR Am J Roentgenol* 2020; **214**: 1445-1452 [PMID: 32319794 DOI: 10.2214/AJR.19.21872]

31 **Adachi M**, Fujioka T, Mori M, Kubota K, Kikuchi Y, Xiaotong W, Oyama J, Kimura K, Oda G, Nakagawa T, Uetake H, Tateishi U. Detection and Diagnosis of Breast Cancer Using Artificial Intelligence Based assessment of Maximum Intensity Projection Dynamic Contrast-Enhanced Magnetic Resonance Images. *Diagnostics (Basel)* 2020; **10** [PMID: 32443922 DOI: 10.3390/diagnostics10050330]

32 **Penco S**, Rotili A, Pesapane F, Trentin C, Dominelli V, Faggian A, Farina M, Marinucci I, Bozzini A, Pizzamiglio M, Ierardi AM, Cassano E. MRI-guided vacuum-assisted breast biopsy: experience of a single tertiary referral cancer centre and prospects for the future. *Med Oncol* 2020; **37**: 36 [PMID: 32221708 DOI: 10.1007/s12032-020-01358-w]

33 **Hu Y**, Zhang Y, Cheng J. Diagnostic value of molybdenum target combined with DCE-MRI in different types of breast cancer. *Oncol Lett* 2019; **18**: 4056-4063 [PMID: 31516606 DOI: 10.3892/ol.2019.10746]

34 **Spick C**, Pinker-Domenig K, Rudas M, Helbich TH, Baltzer PA. MRI-only lesions: application of diffusion-weighted imaging obviates unnecessary MR-guided breast biopsies. *Eur Radiol* 2014; **24**: 1204-1210 [PMID: 24706105 DOI: 10.1007/s00330-014-3153-6]

35 **Sasaki M**, Tozaki M, Rodríguez-Ruiz A, Yotsumoto D, Ichiki Y, Terawaki A, Oosako S, Sagara Y. Artificial intelligence for breast cancer detection in mammography: experience of use of the ScreenPoint Medical Transpara system in 310 Japanese women. *Breast Cancer* 2020; **27**: 642-651 [PMID: 32052311 DOI: 10.1007/s12282-020-01061-8]

36 **Rodriguez-Ruiz A**, Lång K, Gubern-Merida A, Broeders M, Gennaro G, Clauser P, Helbich TH, Chevalier M, Tan T, Mertelmeier T, Wallis MG, Andersson I, Zackrisson S, Mann RM, Sechopoulos I. Stand-Alone Artificial Intelligence for Breast Cancer Detection in Mammography: Comparison With 101 Radiologists. *J Natl Cancer Inst* 2019; **111**: 916-922 [PMID: 30834436 DOI: 10.1093/jnci/djy222]

37 **Shin JH**, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, Lim HK, Moon WJ, Na DG, Park JS, Choi YJ, Hahn SY, Jeon SJ, Jung SL, Kim DW, Kim EK, Kwak JY, Lee CY, Lee HJ, Lee JH, Lee KH, Park SW, Sung JY; Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology. Ultrasonography Diagnosis and Imaging-Based Management of Thyroid Nodules: Revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. *Korean J Radiol* 2016; **17**: 370-395 [PMID: 27134526 DOI: 10.3348/kjr.2016.17.3.370]

38 **Haugen BR**. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: What is new and what has changed? *Cancer* 2017; **123**: 372-381 [PMID: 27741354 DOI: 10.1002/cncr.30360]

39 **Barczyński M**, Stopa-Barczyńska M, Wojtczak B, Czarniecka A, Konturek A. Clinical validation of S-Detect™ mode in semi-automated ultrasound classification of thyroid lesions in surgical office. *Gland Surg* 2020; **9**: S77-S85 [PMID: 32175248 DOI: 10.21037/gs.2019.12.23]

40 **Kim HL**, Ha EJ, Han M. Real-World Performance of Computer-Aided Diagnosis System for Thyroid Nodules Using Ultrasonography. *Ultrasound Med Biol* 2019; **45**: 2672-2678 [PMID: 31262524 DOI: 10.1016/j.ultrasmedbio.2019.05.032]

41 **Lee JH**, Ha EJ, Kim D, Jung YJ, Heo S, Jang YH, An SH, Lee K. Application of deep learning to the diagnosis of cervical lymph node metastasis from thyroid cancer with CT: external validation and clinical utility for resident training. *Eur Radiol* 2020; **30**: 3066-3072 [PMID: 32065285 DOI: 10.1007/s00330-019-06652-4]

42 **Kroenig M**, Schaal K, Benndorf M, Soschynski M, Lenz P, Krauss T, Drendel V, Kayser G, Kurz P, Werner M, Wetterauer U, Schultze-Seemann W, Langer M, Jilg CA. Diagnostic Accuracy of Robot-Guided, Software Based Transperineal MRI/TRUS Fusion Biopsy of the Prostate in a High Risk Population of Previously Biopsy Negative Men. *Biomed Res Int* 2016; **2016**: 2384894 [PMID: 27990424 DOI: 10.1155/2016/2384894]

43 **Raciti P**, Sue J, Ceballos R, Godrich R, Kunz JD, Kapur S, Reuter V, Grady L, Kanan C, Klimstra

DS, Fuchs TJ. Novel artificial intelligence system increases the detection of prostate cancer in whole slide images of core needle biopsies. *Mod Pathol* 2020; **33**: 2058-2066 [PMID: 32393768 DOI: 10.1038/s41379-020-0551-y]

44 **Siddiqui MM**, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, Okoro C, Raskolnikov D, Parnes HL, Linehan WM, Merino MJ, Simon RM, Choyke PL, Wood BJ, Pinto PA. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015; **313**: 390-397 [PMID: 25626035 DOI: 10.1001/jama.2014.17942]

45 **Kasivisvanathan V**, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, Briganti A, Budäus L, Hellawell G, Hindley RG, Roobol MJ, Eggener S, Ghei M, Villers A, Bladou F, Villeirs GM, Virdi J, Boxler S, Robert G, Singh PB, Venderink W, Hadaschik BA, Ruffion A, Hu JC, Margolis D, Crouzet S, Klotz L, Taneja SS, Pinto P, Gill I, Allen C, Giganti F, Freeman A, Morris S, Punwani S, Williams NR, Brew-Graves C, Deeks J, Takwoingi Y, Emberton M, Moore CM; PRECISION Study Group Collaborators. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018; **378**: 1767-1777 [PMID: 29552975 DOI: 10.1056/NEJMoa1801993]

46 **Sanford T**, Harmon SA, Turkbey EB, Kesani D, Tuncer S, Madariaga M, Yang C, Sackett J, Mehralivand S, Yan P, Xu S, Wood BJ, Merino MJ, Pinto PA, Choyke PL, Turkbey B. Deep-Learning-Based Artificial Intelligence for PI-RADS Classification to Assist Multiparametric Prostate MRI Interpretation: A Development Study. *J Magn Reson Imaging* 2020; **52**: 1499-1507 [PMID: 32478955 DOI: 10.1002/jmri.27204]

47 **Reda I**, Khalil A, Elmogy M, Abou El-Fetouh A, Shalaby A, Abou El-Ghar M, Elmaghraby A, Ghazal M, El-Baz A. Deep Learning Role in Early Diagnosis of Prostate Cancer. *Technol Cancer Res Treat* 2018; **17**: 1533034618775530 [PMID: 29804518 DOI: 10.1177/1533034618775530]

48 **Wang X**, Yang W, Weinreb J, Han J, Li Q, Kong X, Yan Y, Ke Z, Luo B, Liu T, Wang L. Searching for prostate cancer by fully automated magnetic resonance imaging classification: deep learning *vs* non-deep learning. *Sci Rep* 2017; **7**: 15415 [PMID: 29133818 DOI: 10.1038/s41598-017-15720-y]

49 **Giovacchini G**, Guglielmo P, Mapelli P, Incerti E, Gajate AMS, Giovannini E, Riondato M, Briganti A, Gianolli L, Ciarmiello A, Picchio M. ^{11}C-choline PET/CT predicts survival in prostate cancer patients with PSA < 1 NG/mL. *Eur J Nucl Med Mol Imaging* 2019; **46**: 921-929 [PMID: 30631911 DOI: 10.1007/s00259-018-4253-3]

50 **Polymeri E**, Sadik M, Kaboteh R, Borrelli P, Enqvist O, Ulén J, Ohlsson M, Trägårdh E, Poulsen MH, Simonsen JA, Hoilund-Carlsen PF, Johnsson ÅA, Edenbrandt L. Deep learning-based quantification of PET/CT prostate gland uptake: association with overall survival. *Clin Physiol Funct Imaging* 2020; **40**: 106-113 [PMID: 31794112 DOI: 10.1111/cpf.12611]

51 **Chauvie S**, De Maggi A, Baralis I, Dalmasso F, Berchialla P, Priotto R, Violino P, Mazza F, Melloni G, Grosso M; SOS Study team. Artificial intelligence and radiomics enhance the positive predictive value of digital chest tomosynthesis for lung cancer detection within SOS clinical trial. *Eur Radiol* 2020; **30**: 4134-4140 [PMID: 32166491 DOI: 10.1007/s00330-020-06783-z]

52 **Tau N**, Stundzia A, Yasufuku K, Hussey D, Metser U. Convolutional Neural Networks in Predicting Nodal and Distant Metastatic Potential of Newly Diagnosed Non-Small Cell Lung Cancer on FDG PET Images. *AJR Am J Roentgenol* 2020; **215**: 192-197 [PMID: 32348182 DOI: 10.2214/AJR.19.22346]

53 **Yu JY**, Zhang HP, Tang ZY, Zhou J, He XJ, Liu YY, Liu XJ, Guo DJ. Value of texture analysis based on enhanced MRI for predicting an early therapeutic response to transcatheter arterial chemoembolisation combined with high-intensity focused ultrasound treatment in hepatocellular carcinoma. *Clin Radiol* 2018; **73**: 758.e9-758. e18 [PMID: 29804627 DOI: 10.1016/j.crad.2018.04.013]

54 **Peng J**, Kang S, Ning Z, Deng H, Shen J, Xu Y, Zhang J, Zhao W, Li X, Gong W, Huang J, Liu L. Residual convolutional neural network for predicting response of transarterial chemoembolization in hepatocellular carcinoma from CT imaging. *Eur Radiol* 2020; **30**: 413-424 [PMID: 31332558 DOI: 10.1007/s00330-019-06318-1]

55 **Khan MJ**, Werner CL, Darragh TM, Guido RS, Mathews C, Moscicki AB, Mitchell MM, Schiffman M, Wentzensen N, Massad LS, Mayeaux EJ Jr, Waxman AG, Conageski C, Einstein MH, Huh WK. ASCCP Colposcopy Standards: Role of Colposcopy, Benefits, Potential Harms, and Terminology for Colposcopic Practice. *J Low Genit Tract Dis* 2017; **21**: 223-229 [PMID: 28953110 DOI: 10.1097/LGT.0000000000000338]

56 **Mayeaux EJ Jr**, Novetsky AP, Chelmow D, Garcia F, Choma K, Liu AH, Papasozomenos T, Einstein MH, Massad LS, Wentzensen N, Waxman AG, Conageski C, Khan MJ, Huh WK. ASCCP Colposcopy Standards: Colposcopy Quality Improvement Recommendations for the United States. *J Low Genit Tract Dis* 2017; **21**: 242-248 [PMID: 28953113 DOI: 10.1097/LGT.0000000000000342]

57 **Brown BH**, Tidy JA. The diagnostic accuracy of colposcopy - A review of research methodology and impact on the outcomes of quality assurance. *Eur J Obstet Gynecol Reprod Biol* 2019; **240**: 182-186 [PMID: 31302386 DOI: 10.1016/j.ejogrb.2019.07.003]

58 **Xue P**, Ng MTA, Qiao Y. The challenges of colposcopy for cervical cancer screening in LMICs and solutions by artificial intelligence. *BMC Med* 2020; **18**: 169 [PMID: 32493320 DOI: 10.1186/s12916-020-01613-x]

59 **Wolz R**, Chu C, Misawa K, Fujiwara M, Mori K, Rueckert D. Automated abdominal multi-organ segmentation with subject-specific atlas generation. *IEEE Trans Med Imaging* 2013; **32**: 1723-1730 [PMID: 23744670 DOI: 10.1109/TMI.2013.2265805]

60 **Summers RM**, Elton DC, Lee S, Zhu Y, Liu J, Bagheri M, Sandfort V, Grayson PC, Mehta NN,

Pinto PA, Linehan WM, Perez AA, Graffy PM, O'Connor SD, Pickhardt PJ. Atherosclerotic Plaque Burden on Abdominal CT: Automated Assessment With Deep Learning on Noncontrast and Contrast-enhanced Scans. *Acad Radiol* 2020 [PMID: 32958429 DOI: 10.1016/j.acra.2020.08.022]

61 **Wang G**, Li W, Zuluaga MA, Pratt R, Patel PA, Aertsen M, Doel T, David AL, Deprest J, Ourselin S, Vercauteren T. Interactive Medical Image Segmentation Using Deep Learning With Image-Specific Fine Tuning. *IEEE Trans Med Imaging* 2018; **37**: 1562-1573 [PMID: 29969407 DOI: 10.1109/TMI.2018.2791721]

62 **Boers TGW**, Hu Y, Gibson E, Barratt DC, Bonmati E, Krdzalic J, van der Heijden F, Hermans JJ, Huisman HJ. Interactive 3D U-net for the segmentation of the pancreas in computed tomography scans. *Phys Med Biol* 2020; **65**: 065002 [PMID: 31978921 DOI: 10.1088/1361-6560/ab6f99]

63 **Halverson SJ**, Kunju LP, Bhalla R, Gadzinski AJ, Alderman M, Miller DC, Montgomery JS, Weizer AZ, Wu A, Hafez KS, Wolf JS Jr. Accuracy of determining small renal mass management with risk stratified biopsies: confirmation by final pathology. *J Urol* 2013; **189**: 441-446 [PMID: 23253955 DOI: 10.1016/j.juro.2012.09.032]

64 **Dagher J**, Delahunt B, Rioux-Leclercq N, Egevad L, Srigley JR, Coughlin G, Dunglinson N, Gianduzzo T, Kua B, Malone G, Martin B, Preston J, Pokorny M, Wood S, Yaxley J, Samaratunga H. Clear cell renal cell carcinoma: validation of World Health Organization/International Society of Urological Pathology grading. *Histopathology* 2017; **71**: 918-925 [PMID: 28718911 DOI: 10.1111/his.13311]

65 **Delahunt B**, Eble JN, Egevad L, Samaratunga H. Grading of renal cell carcinoma. *Histopathology* 2019; **74**: 4-17 [PMID: 30565310 DOI: 10.1111/his.13735]

66 **Kim H**, Inomoto C, Uchida T, Furuya H, Komiyama T, Kajiwara H, Kobayashi H, Nakamura N, Miyajima A. Verification of the International Society of Urological Pathology recommendations in Japanese patients with clear cell renal cell carcinoma. *Int J Oncol* 2018; **52**: 1139-1148 [PMID: 29532874 DOI: 10.3892/ijo.2018.4294]

67 **Zhao J**, Zhang P, Chen X, Cao W, Ye Z. Lesion Size and Iodine Quantification to Distinguish Low-Grade From High-Grade Clear Cell Renal Cell Carcinoma Using Dual-Energy Spectral Computed Tomography. *J Comput Assist Tomogr* 2016; **40**: 673-677 [PMID: 27224223 DOI: 10.1097/RCT.0000000000000441]

68 **Parada Villavicencio C**, Mc Carthy RJ, Miller FH. Can diffusion-weighted magnetic resonance imaging of clear cell renal carcinoma predict low from high nuclear grade tumors. *Abdom Radiol (NY)* 2017; **42**: 1241-1249 [PMID: 27904923 DOI: 10.1007/s00261-016-0981-7]

69 **Aslan A**, İnan İ, Aktan A, Ayaz E, Aslan M, Özkanlı SŞ, Yıldırım A, Yıkılmaz A. The utility of ADC measurement techniques for differentiation of low- and high-grade clear cell RCC. *Pol J Radiol* 2018; **83**: e446-e451 [PMID: 30655922 DOI: 10.5114/pjr.2018.80207]

70 **Chen C**, Kang Q, Xu B, Guo H, Wei Q, Wang T, Ye H, Wu X. Differentiation of low- and high-grade clear cell renal cell carcinoma: Tumor size versus CT perfusion parameters. *Clin Imaging* 2017; **46**: 14-19 [PMID: 28686936 DOI: 10.1016/j.clinimag.2017.06.010]

71 **Cui E**, Li Z, Ma C, Li Q, Lei Y, Lan Y, Yu J, Zhou Z, Li R, Long W, Lin F. Predicting the ISUP grade of clear cell renal cell carcinoma with multiparametric MR and multiphase CT radiomics. *Eur Radiol* 2020; **30**: 2912-2921 [PMID: 32002635 DOI: 10.1007/s00330-019-06601-1]

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AIMS AND SCOPE

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

AIC mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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MINIREVIEWS

Therapeutic tumor vaccines — a rising star to benefit cancer patients

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Abstract

Malignant tumors are still a worldwide threat to human health. Tumor treatment strategies are constantly evolving, and the advent of tumor immunotherapy has brought up hope to many types of tumors, especially for those that are refractory to conventional therapies including surgery, radiotherapy, and chemotherapy. Tumor vaccines can initiate or amplify an anti-tumor immune response in tumor patients through active immunization, and therefore occupy an important position in tumor immunotherapy. The main types of tumor vaccines include tumor cell vaccines, dendritic cell vaccines, polypeptide vaccines and nucleic acid vaccines. Due to factors such as poor antigen selection and suppressive tumor microenvironment, earliest tumor vaccines on clinical trials failed to achieve satisfactory clinical effects. However, with the development of second-generation genome sequencing technologies and bioinformatics tools, it is possible to predict neoantigens generated by tumor-specific mutations and therefore prepare personalized vaccines. This article summarizes the global efforts in developing tumor vaccines and highlights several representative tumor vaccines in each category.

Key Words: Tumor vaccines; Tumor cell vaccines; Dendritic cell vaccines; Peptide vaccines; Nucleic acid vaccines

Core Tip: There are many advancements in the field of cancer immunotherapy in the past decade such as the application of immune checkpoint blockade and adoptive cell therapy. Tumor therapeutic vaccines have emerged as an additional effective treatment

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strategy due to their ability to trigger potent immune response. Typically, they are tumor cell vaccines, dendritic cell vaccines, peptide vaccines or nucleic acid vaccines. This article mainly reviews the current clinical status as well as research and development status of these four types of therapeutic tumor vaccines for those who are interested.

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INTRODUCTION

Exploratory research on tumor vaccines can be traced back to 1891 when Dr. William B. Coley first proved that heat-inactivated *Streptococcus pyogenes* and *Serratia marcescens* (Coley toxin) are effective treatments for inoperable tumors[1]. Coley toxin is especially effective for osteosarcoma and soft tissue sarcoma, thus inspiring the subsequent development of various tumor vaccines. While Coley toxin has faded out of clinical application, its pioneering role cannot be erased. Therapeutic tumor vaccines represent a viable option for tumor immunotherapy, which aims to stimulate the patient's immune system to specifically kill tumor cells without damaging normal cells[2]. Therapeutic cancer vaccines are designed to induce enduring anti-tumor immunity, which enables active immunity to systematically prevent tumor recurrence or metastatic disease. Research on the exploration of approaches to therapeutic tumor vaccines has been ongoing and has been achieving varying degrees of success[3]. So far, the United States Food and Drug Administration (FDA) has approved the following two types of preventive tumor vaccines: Hepatitis B virus (HBV) vaccine-a recombinant HBV vaccine Recombivax HB® approved in 1983 and Engerix-B® approved in 1989, and human papillomavirus (HPV) vaccine: Recombinant HPV type 6, 11, 16, 18 (Gardasil®), recombinant HPV 9-valent vaccine (Gardasil® 9) and recombinant HPV type 16, 18 (Cervarix®).

Compared with preventive tumor vaccines, therapeutic tumor vaccine development has lagged significantly. In terms of therapeutic tumor vaccines, the United States FDA so far only approved sipuleucel-T (Provenge®) in 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (CRPC) and an oncolytic virus-based vaccine talimogene laherparepvec for the treatment of advanced melanoma in 2015[4,5]. Other countries have also approved 5 therapeutic tumor vaccines, which are DCVax®-Brain and M-Vax™ approved by Switzerland, HybriCell approved by Brazil, Oncophage® approved by Russia and CIMAVax EGF® approved by Cuba and Peru[6]. However, 4 out of these 5 tumor vaccines (DCVax®-Brain, M-Vax™, HybriCell and CIMAVax EGF®) had simply completed phase I and II clinical trials by the time of approval. The main goal of Oncophage®'s phase III clinical trial is to prolong relapse-free survival (RFS) and overall survival (OS) instead of efficacy. According to the data retrieved from ClinicalTrials.gov, there are 439 "therapeutic cancer vaccines" under development worldwide, of which North America accounts for the largest proportion of 301 (Figure 1, Source: https://ClinicalTrials.gov). This article mainly summarizes some tumor vaccines that have entered phase III clinical trials. Some tumor vaccines that are currently under recruitment in early clinical trials phase I and II are listed in Table 1.

TUMOR CELL VACCINES

The original tumor cell vaccine tends to fail to induce a strong immune response. In order to change this deficiency, molecular modification techniques have been employed to change the immune characteristics or genetic background of tumor cells to improve their immunogenicity and generate a stronger immune response. Tumor cell vaccine is a whole tumor cell vaccine containing a series of antigens prepared from surgically removed tumor tissues. The removed tumor tissues are minced to tumor cells which are usually inactivated by radiation in the laboratory so that they no longer

Table 1 Selected list of tumor vaccine under recruitment in clinical trials

Vaccine type		Disease	Combination	Phase	NCT ID
Tumor cell vaccine	GVAX	Neuroblastoma. Pediatric Solid Tumor	Nivolumab. Ipilimumab	Phase I	NCT04239040
		Locally Advanced Pancreatic Ductal Adenocarcinoma	Nivolumab CCR2/CCR5 dual antagonist	Phase I; Phase II	NCT03767582
		Metastatic Pancreatic Adenocarcinoma	Epacadostat. Pembrolizumab CRS-207 CY	Phase II	NCT03006302
		Colorectal Cancer		Phase I	NCT01952730
	GVAX Pancreas Vaccine	Pancreatic Cancer	Cyclophosphamide Nivolumab	Phase II	NCT03161379
		Pancreatic Cancer	Cyclophosphamide Nivolumab Urelumab	Phase I; Phase II	NCT02451982
	GM-CSF vaccine	Multiple Myeloma	Lenalidomide Prevnar13	Phase II	NCT03376477
DC Vaccine	AST-VAC2	NSCLC in the Advanced and Adjuvant Settings		Phase I	NCT03371485
	MIDRIXNEO	NSCLC	Antigen-specific DTH. Control DTH	Phase I	NCT04078269
	Autologous Dendritic Cell-Adenovirus CCL21 Vaccine	NSCLC Stage IV, IVA, IVB Lung Cancer AJCC v8	Pembrolizumab	Phase I	NCT03546361
	Autologous DCs: MESOVAX	Mesothelioma. Malignant PD-L1 Negative Advanced Cancer Progressive Disease	Pembrolizumab. Interleukin-2	Phase I	NCT03546426
	PEP-DC vaccine	Pancreatic Adenocarcinoma		Phase I	NCT04627246
	ME TARP vaccine	Prostate Cancer		Phase II	NCT02362451
	DC/AML Fusion Vaccine	Acute Myelogenous Leukemia	Decitabine	Phase I	NCT03679650
		Acute Myelogenous Leukemia		Phase II	NCT03059485
	mDC3/8-KRAS Vaccine	Pancreatic Ductal Adenocarcinoma		Phase I	NCT03592888
	Autologous DC vaccine: RaC-Ad	Head Neck Tumors, Neuroendocrine Tumors, Soft Tissue Sarcoma Rare Cancer	Interleukin-2	Phase II	NCT04166006
	COREVAX-1	Stage IV Colorectal Cancer Curative Resection	Interleukin-2	Phase II	NCT02919644
	Autologous DCs + Prevnar 13	Stage III, IIIA, IIIB, IV, IVA, IVB Hepatocellular Carcinoma AJCC v8, Stage III, IIIA, IIIB, IV Intrahepatic Cholangiocarcinoma AJCC v8, Unresectable Hepatocellular Carcinoma, Unresectable Intrahepatic Cholangiocarcinoma	Radiation: External Beam Radiation Therapy	Early Phase I	NCT03942328
	DC Tumor Cell Lysate Vaccine: ATL-DC	Recurrent Glioblastoma	Pembrolizumab poly-ICLC	Phase I	NCT04201873
	Dendritic Cell/Tumor Fusion Vaccine	Glioblastoma, Neuroectodermal Tumors	Interleukin-12 Temozolomide	Phase I; Phase II	NCT04388033
	DC1 Vaccine+ WOKVAC Vaccine	Female Breast Cancer, Male Breast Cancer, Stage I, II, III Breast Cancer, HER2-positive Breast Cancer		Phase II	NCT03384914
	neoantigen-primed DC vaccine	Gastric Cancer, Hepatocellular Carcinoma, NSCLC, Colon Rectal Cancer		Phase I	NCT04147078
	MG-7-DC vaccine	Later stage of gastric cancer	Sintilimab	Phase I; Phase II	NCT04567069
	IKKb matured, RNA-loaded DC vaccine	Melanoma, Uveal Metastatic		Phase II	NCT04335890
Peptide vaccine	UCPVax: VolATIL	Squamous Cell Carcinoma of the Head and Neck, Anal Canal Cancer, Cervical Cancer	Atezolizumab	Phase II	NCT03946358
	UCPVax-Glio	Glioblastoma		Phase I; Phase II	NCT04280848
	UCPVax	Metastatic NSCLC		Phase I; Phase II	NCT02818426
	MUC1	NSCLC	PolyICLC	Phase I; Phase II	NCT01720836

	SVN53-67/M57-KLH	Lung Atypical Carcinoid Tumor, Lung Typical Carcinoid Tumor, Metastatic Pancreatic Neuroendocrine Tumor	Incomplete Freund's Adjuvant Octreotide Acetate Sargramostim	Phase I	NCT03879694
	NSABP FB-14/AE37	Triple-negative Breast Cancer	Pembrolizumab	Phase II	NCT04024800
	KRAS peptide vaccine	Colorectal Cancer, Pancreatic Cancer	Nivolumab Ipilimumab	Phase I	NCT04117087
	da VINc/OTSGC-A24	Gastric Cancer	Nivolumab Ipilimumab	Phase I	NCT03784040
	ARG1-18, 19, 20	NSCLC, Urothelial Carcinoma, Malignant Melanoma, Ovarian Cancer, Colorectal Cancer, Breast Cancer, Squamous Cell Carcinoma of the Head and Neck, Metastatic Cancer		Phase I	NCT03689192
	Personalized peptide vaccine	Stage IV, IVA, IVB Colorectal Cancer AJCC v7, Stage IV Pancreatic Cancer AJCC v6 and v7	Imiquimod Pembrolizumab	Phase I	NCT02600949
	WT1/NY-ESO-1	Ovarian Cancer, Fallopian Tube Primary Peritoneal Cancer, Recurrent Ovarian Cancer	Nivolumab	Phase I	NCT02737787
	IMU-131/HER-Vaxx	Gastrointestinal Neoplasms, Adenocarcinoma	Cisplatin and either Fluorouracil (5-FU) or Capecitabine or Oxaliplatin and capecitabine	Phase I; Phase II	NCT02795988
	ESR1	Breast Cancer		Phase I	NCT04270149
	DNAJB1-PRKACA	Fibrolamellar, Hepatocellular Carcinoma	Nivolumab Ipilimumab	Phase I	NCT04248569
	H3.3K27M	Diffuse Intrinsic Pontine Glioma, Diffuse Midline Glioma, H3 K27M-Mutant	Nivolumab	Phase I; Phase II	NCT02960230
	H2NVAC	Ductal Breast Carcinoma In Situ	Granulocyte Macrophage Colony Stimulating Fator	Phase I	NCT04144023
	IDH1R132H/AMPLIFY-NEOVAC	Malignant Glioma	Avelumab	Phase I	NCT03893903
DNA Vaccine	pTVG-HP/pTVG-AR	CRPC, Metastatic Cancer	Pembrolizumab rhGM-CSF	Phase II	NCT04090528
	Mammaglobin-A	Breast Cancer		Phase I	NCT02204098
	pTVG-HP	Prostate Cancer	Nivolumab GM-CSF	Phase II	NCT03600350
	pNGVL4a-Sig/E7(detox)/HSP70	Cervical Cancer, Precancerous Condition, HPV Disease, Human Papilom-virus	Imiquimod	Phase I	NCT00788164
	Salmonella oral vaccine	Relapsed Neuroblastoma	Lenalidomide	Early Phase I	NCT04049864

NSCLC: Non-small cell lung cancer; CRPC: Castration-resistant prostate cancer; AJCC: American Joint Committee on Cancer; GM-CSF: Granulocyte-macrophage colony stimulating factor.

have proliferative activity even after being imported into the human body. Tumor cell vaccines are basically divided into two types, namely autologous tumor cell vaccines and allogeneic tumor cell vaccines[7,8]. Autologous tumor cell vaccines are prepared by extracting tumor cells from the tumor tissues of patients receiving treatment. They have the advantages of carrying relatively complete known and unknown tumor antigens and not being restricted by major histocompatibility complex (MHC), thus avoiding the immune escape of tumor cells caused by the loss of certain antigens during the process of tumor progression. However, the vaccine made by inactivating tumor cells is extremely weak in immunogenicity and incapable of inducing sufficient anti-tumor immune effects. Allogeneic tumor cell vaccines are prepared using specific types of tumor cells from some other patients instead of the tumor cells from the patients receiving treatment themselves. These allogeneic tumor cell vaccines are more often used as off-the-shelf medicines. Some allogeneic tumor cell vaccines are prepared from mixed tumor cells extracted from tumor cells of several patients[8].

OncoVAX®

OncoVAX® is an autologous tumor cell vaccine developed using patients' autologous colorectal cancer cells and is used for adjuvant treatment of patients after colorectal cancer resection. The vaccine is a patient's autologous tumor cell vaccine that combines non-proliferative and non-tumorigenic autologous tumor cells with metabolic activity after irradiation and adjuvant of live attenuated TICE strain of bacillus Calmette-Guerin. The company Vaccinogen uses a patented method to extract and purify tumor

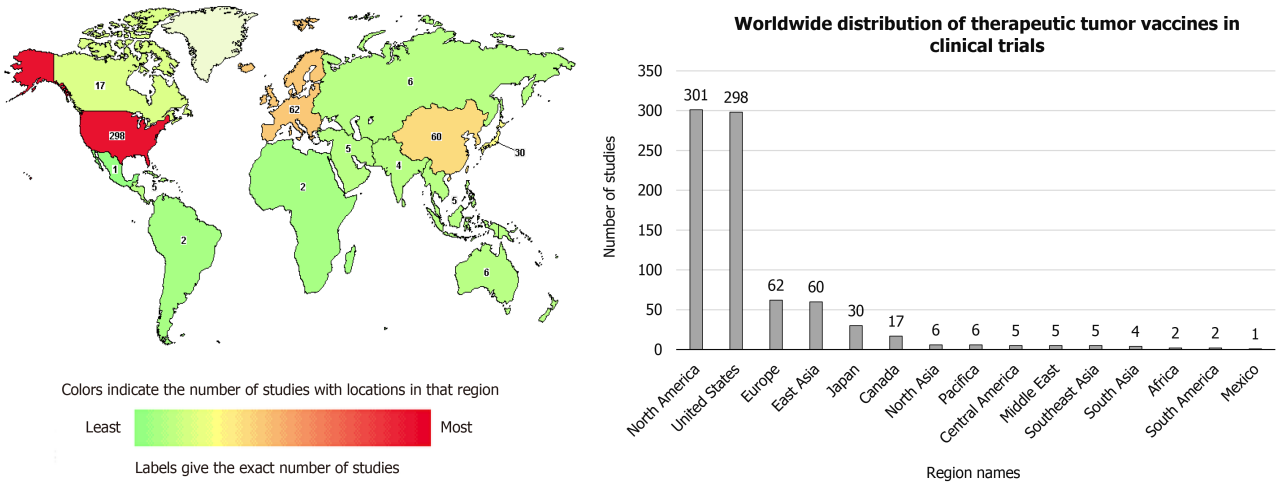

Figure 1 According to resources downloaded from the open access website (https://ClinicalTrials.gov, cited April 9, 2021), clinical trials of tumor vaccines are unevenly distributed in the world, with the United States occupying the largest proportion, followed by Europe and East Asia. Overall, the number of North America far exceeds that of the rest regions in the world. There is little difference in the number of clinical trials conducted in other regions.

cells from the resected colorectal cancer tissue, and then undergo radiation treatment, and then inoculate them to the patient to produce an effective and personalized immune response to the residual cancer cells that may still exist in the patient after the operation.

Vermorken *et al*[9] investigated the effect of OncoVAX® on 254 patients with stage II and III colon cancer in a randomized phase III clinical trial, and they published their results on the lancet. The patients were randomly divided into surgery group (control group, 126 cases) and surgery + vaccine group (treatment group, 128 cases). The median follow-up period was 5.3 years (8-107 mo). Among the tested patients, 65 patients relapsed, including 25 patients in the treatment group and 40 patients in the control group; the risk of recurrence of patients in the treatment group was reduced [risk ratio (RR) = 44%, 95% confidence interval (CI): 7%-66%, P = 0.023]. In the patient staging analysis, OncoVAX® had no significant effect on patients with stage III colon cancer, but it could significantly prolong the recurrence-free period of patients with stage II colon cancer (P = 0.011), and the overall risk of recurrence was reduced (RR = 61%, 95%CI: 18%-81%), the RFS of patients in the treatment group was significantly prolonged [the risk of recurrence or death was reduced (RR = 42%, 95%CI: 0%-68%, P = 0.032)].

5 clinical studies of OncoVAX®, including the study above, which established optimum dose and regimen, have been completed by 2014. 757 subjects with colorectal cancer, of which 720 had colon cancer, have been enrolled in OncoVAX® trials[10]. In addition, the results of the follow-up bioequivalent study (NCT00016133) involving 15 subjects with cGMP-level manufacturing standard concluded the immunogenicity of OncoVAX® was unaffected by the sterilization process[11]. OncoVAX® has reached a Special Protocol Assessment with the FDA and has been granted Fast Track status by the FDA. The phase IIIb clinical trial (NCT02448173) is under recruitment currently which is expected to be completed in July 2022.

Gemogenovatucel-T

Gemogenovatucel-T (FANG, Vigil™) is a whole autologous tumor cell vaccine developed by Gradalis Inc., which incorporates plasmid-encoded granulocyte-macrophage colony stimulating factor and a bifunctional small hairpin RNA interference vector targeting furin converting enzyme. Senzer *et al*[12] conducted a phase I clinical trial on patients with advanced tumors and demonstrated the long-term safety of the vaccine and the effect of inducing circulated and activated T cells against tumor cells during a 3-year follow-up.

Based on its safety, immunoeffectiveness, and suggested benefits previously verified, Nemunaitis *et al*[13] provided a follow-up study of a subset of 8 advanced hepatocellular carcinoma patients and demonstrated that no obvious toxicity was observed and a significant induction of systemic immune response. In the phase II clinical trial of patients with advanced ovarian cancer, the reaction with interferon-γ

(IFN-γ) enzyme-linked immunospot assay (ELISPOT) before Gemogenovatucel-T vaccination serves as the baseline [negative rate: About 97% (30/31)]. In contrast, the IFN-γ ELISPOT reaction of the patient after vaccination was 100% (31/31) positive, and the circulating activated T cell population that induced by the autologous tumor cells was significantly expanded. In addition, the average RFS of the vaccinated group was 826 d with a median of 604 d, while the control group had an average RFS of 481 d with a median of 377 d (P = 0.033)[14].

Rocconi *et al*[15] has carried out a study (ClinicalTrials.gov, NCT02346747), in which 91 eligible patients with stage III or IV high-grade serous, endometrioid, or clear cell ovarian cancer were randomly assigned to receive Gemogenovatucel-T (n = 47) or placebo (n = 44). Recurrence-free survival was 11.5 mo (95%CI: 7.5-not reached) for patients assigned to Gemogenovatucel-T *vs* 8.4 mo (7.9-15.5) for patients assigned to placebo [hazard ratio (HR) 0.69, 90%CI: 0.44-1.07; one-sided P = 0.078]. According to the results, no grade 3 or 4 toxic events was reported among the Gemogenovatucel-T arm. Serious adverse events were reported in 4 patients in the placebo arm and 3 patients in the Gemogenovatucel-T arm. No treatment-related deaths occurred in either group[15].

Rocconi *et al*[16] posted the data of the double-blind, placebo-controlled trial in phase IIb. Patients were in complete response with Stage III/IV high grade serious, endometroid or clear cell ovarian cancer. Results demonstrated clinical benefit in homologous recombination proficient (HRP) ovarian cancer. RFS was improved with Vigil (n = 25) in HRP patients compared to placebo (n = 20) (HR = 0.386; 90%CI: 0.199-0.750; P = 0.007), results were verified by Rhabdomyosarcoma 2-Associated Transcript (RMST) (P = 0.017). Similarly, OS benefit was observed in Vigil group compared to placebo (HR = 0.342; 90%CI: 0.141-0.832; P = 0.019). Results with OS were also verified with RMST (P = 0.008)[16].

DENDRITIC CELL VACCINES

Dendritic cell (DC) is widely recognized as the most powerful full-time antigen-presenting cell since its antigen-presenting ability is hundreds of times higher compared with other antigen presenting cells. The development of DC vaccines is still at an early stage, but a large amount of valuable experimental data has been obtained showing that DC exerts a powerful function in antigen presentation and initiating anti-tumor immunity. DC-based immunotherapy has been used to generate tumor cytotoxic T cells, which is an effective means to fight tumor cells[17-20]. So far, the United States FDA has only approved one DC vaccine sipuleucel-T for the treatment of metastatic CRPC; Switzerland and Brazil approved two DC vaccines- DCVax®-Brain for the treatment of brain tumors and HybriCell for the treatment of kidney cancer and melanoma[6].

Stapuldencel-T

Stapuldencel-T (DCVAC/PCa) is a vaccine which a Czech biotech company (Sotio a.s.) uses autologous leukocytes obtained from prostate cancer patients during the leukapheresis process as raw material to grow immature DCs *in vitro*. The high hydrostatic pressure kills the immunogenic tumor cells which sensitize the immature DCs and make them mature. The loaded mature DCs are then be inoculated into prostate cancer patients. Podrazil *et al*[21] conducted a phase I/II clinical trial (EudraCT 2009-017295-24) of combining DCVAC/PCa and docetaxel to treat 25 patients with metastatic CRPC, the median OS (mOS) of the subjects was 19 mo, which is obviously longer than the mOS of 11.8 and 13 mo predicted by Halabi nomogram and MSKCC nomogram, respectively. There were no DCVAC/PCa-related adverse reactions. Long-term vaccination with DCVAC/PCa can induce and maintain the growth of prostate-specific antigen (PSA)-specific T cells. Fucikova *et al*[22] conducted a phase I/II trial (EudraCT 2009-017259-91) involving 27 patients with rising PSA levels. The median PSADT (PSA doubling time) in all treated patients increased from 5.67 mo prior to immunotherapy to 18.85 mo after 12 doses (P < 0.0018). Moreover, specific PSA-reacting T lymphocytes were increased significantly already after the 4th dose.

Sotio has accomplished 5 earlier trials of DCVAC/PCa in prostate cancer at varying stages namely SP001 (NCT02105675), SP002 (NCT02107391), SP003 (NCT02107404), SP004 (NCT02107430), SP010 (NCT02137746). Based on previous trials, it launched an extensive global multi-center phase III clinical trial studying DCVAC/PCa in prostate cancer (SP005:NCT02111577) to determine whether DCVAC/PCa added onto

standard of care (SOC) therapy can improve survival rate. The VIABLE study (actiVe ImmunotherApy using DC-Based treatment for late stage prostatE cancer) enrolled 1182 prostate cancer patients across 21 European countries and the United States. As of January 21, 2021, results of VIABLE study were submitted to United States trial registry but have not yet been announced. However, SOTIO terminates the phase I/II SP015 trial (NCT03514836; EudraCT2015-004314-15) in prostate cancer in Czech Republic owing to insufficient patient accrual.

Rocapuldencel-T

Rocapuldencel-T (AGS-003) is a mature monocyte-derived DC vaccine developed by Argos Therapeutics, Inc. using patients' own amplified tumor RNA plus synthetic CD40L RNA for electroporation, which induces the activation and expansion of new T cells (including persistent memory cells and killer cells) based on Arcelis technology platform, specifically attacking the unique antigens of each patient's tumor. Amin *et al* [23] carried out a phase II clinical trial that combined AGS-003 and sunitinib in 21 patients with advanced renal cell carcinoma (RCC). The results showed that 13 patients (62%) were effective in this therapy (9 patients responded and 4 patients were in stable condition), but none of the patients achieved complete remission. The median progression-free survival (PFS) of all patients was 11.2 mo (95%CI: 6.0-19.4), and the mOS was 30.2 mo (95%CI: 9.4-57.1); 7 patients (33%) survived at least 4.5 years, 5 cases (24%) survived for more than 5 years, including 2 cases in the continuous response period without disease progression at the completion of the report; the patients tolerated AGS-003 well, and only mild adverse reactions occurred at the vaccination site.

The ADAPT trial recruited 462 patients that were randomized 2:1, 307 to the combination group and 155 to the SOC group between 2013 and 2016. mOS in the combination group was 27.7 mo (95%CI: 23.0-35.9) and 32.4 mo (95%CI: 22.5-not reached) in the SOC group HR of 1.10 (95%CI: 0.83-1.40). PFS was 6.0 mo and 7.83 mo for the combination and SOC groups, respectively [HR = 1.15 (95%CI: 0.92-1.44)]. The ORR was 42.7% (95%CI: 37.1-48.4) for the combination group and 39.4% (95%CI: 31.6-47.5) for the SOC group. Median follow up was 29 mo (0.4-47.7 mo). On account of the lack of clinical efficacy, the ADAPT trial was terminated on February 17, 2017. Immune responses were detected in 70% of patients treated with Rocapuldencel-T, and the magnitude of the immune response positively correlated with OS. Figlin *et al* [24] has conducted the phase III trial to investigate the safety and efficacy of a combination therapy dosing regimen of Rocapuldencel-T plus sunitinib in patients with metastatic RCC. The results indicated that the combination therapy did not improve the patient's OS. Nevertheless, the phase III trial identified two potential survival-predictive biomarkers namely interleukin (IL)-12 produced by the DC vaccine and higher numbers of T regulatory cells present in the peripheral blood of advanced RCC patients.

DCVax®–L

DCVax® was developed and is being commercialized by Northwest Biotherapeutics, Inc. (MD, United States), serving as a platform technology that uses activated autologous DCs to reinvigorate and educate the immune system to attack cancers. DCVax®-L) is designed to cover all solid tumor cancers in which the tumors can be surgically removed. Theoretically, DCVax®-L induces the differentiation and maturation of peripheral blood mononuclear cells into DCs, which are activated and loaded with biomarkers (specific antigens) obtained from the patient's own tumor tissue. Antigens can be derived from autologous tumor lysates as in DCVax®-L for glioblastoma multiforme (GBM) or specific recombinant antigenic epitopes[25,26]. The loading of biomarkers into the DCs "educates" them about what the immune system needs to attack. The activated, educated DCs are then isolated with very high purity and comprise the DCVax®-L personalized vaccine[26].

A 348-patient double blind, randomized, placebo-controlled phase III clinical trial (NCT00045968) with DCVax®-L for newly diagnosed GBM is being implemented, whose enrollment completed in 2015. The primary endpoint of the trial is PFS, and secondary endpoints include OS and other measures. The trial is under way at 51 sites (medical centers) across the United States. Liau *et al*[27] posted its first results on survival indicating that addition of DCVax®-L to standard therapy is feasible and safe in glioblastoma patients and may extend survival. mOS was 23.1 mo from surgery without DCVax®-L. As of this analysis involving 331 patients in 2018, 223 patients are ≥ 30 mo past their surgery date; 67 of these (30.0%) have lived ≥ 30 mo and have a Kaplan-Meier-derived mOS of 46.5 mo. 182 patients are ≥ 36 mo past surgery; 44 of these (24.2%) have lived ≥ 36 mo and have a KM-derived mOS of 88.2 mo[27].

PEPTIDE VACCINES

Peptide vaccines that initially targeted tumor enriched antigens can be classified into two distinct categories: Tumor-associated antigens (TAA) and tumor-specific neoantigens antigens[28,29]. Tumor neoantigen is a specific peptide epitope of tumor cells that can be recognized by T cells due to gene mutations in tumor cells, which can activate T cells and exert anti-tumor immune responses. Currently, Peptide vaccines are mainly used in patients with advanced tumors, and clinical trials have been carried out for patients with CRPC, lung cancer, gastrointestinal tumors, cholangiocarcinoma, pancreatic cancer and GBM. Most of the peptide vaccine research is currently in phase I and phase II clinical trials.

Seviprotimut-L

Seviprotimut-L (POL-103A) is currently in orphan drug status and developed by Polynoma Lewis Lung Carcinoma (LLC), which is a combination of shed antigens produced by three proprietary melanoma cell lines. Polynoma LLC announced the start of Melanoma Antigen Vaccine Immunotherapy Study (MAVIS), the company's phase III trial of POL-103A vaccine for melanoma in June 2012. MAVIS (NCT01546571), a global, multi-center, double-blind, placebo-controlled study, is expected to recruit 1224 participants with resected stage IIb, IIc or III melanoma and a high risk of recurrence. The trial is expected to be initially completed on January 1, 2025[30].

Tedopi® (OSE-2101, EP-2101, IDM-2101)

Tedopi® is a synthetic peptide vaccine developed by the French company OSE Immunotherapeutics, which is a specific treatment for HLA-A2+ patients, a key receptor for the cytotoxic T-immune response, through its proprietary combination of 9 optimized neo-epitopes plus one epitope giving universal helper T cell response targeting T cell activation. Currently, Tedopi® is being investigated in two major cancer indications: Non-small cell lung cancer (NSCLC) with an ongoing phase III trial and pancreatic cancer with an ongoing phase II trial[31].

In February 2016, OSE Immunotherapeutics launched the phase III clinical trial (NCT02654587) named Atalante 1 that compared OSE-2101 as a second and third-line drug with docetaxel or pemetrexed for HLA A2+ IIIB or IV NSCLC patients after immune checkpoint inhibitor (CPI)s [programmed death 1 (PD1)/programmed death-ligand 1] failure. The trial included 99 HLA-A2-positive patients with stage IIIB or metastatic stage IV. They were randomly divided into Tedopi® vaccine treatment group or chemotherapy group (pemetrexed or docetaxel) at a ratio of 2:1. The trial is expected to be completed in December 2021 and was initially completed in February 2020. According to the positive step-1 phase III results announced at the European Society for Medical Oncology Virtual Congress 2020, among the 63 patients in the Tedopi® group, 29 patients survived at least 12 mo and the 12-mo survival rate was 46% higher than expected 25%. In the chemotherapy control group, 13 of the 36 patients survived at least 12 mo, which is equivalent to a 12-mo survival rate of 36% [32].

In previous phase II clinical trials of IDM-2101, this vaccine also achieved promising data.

IDM-2101 (previously EP-2101) was administered for a total of 63 patients positive for HLA-A2 every 3 wk for the first 15 wk, then every 2 mo through year 1, then quarterly through year 2, for a total of 13 doses. Results showed that one-year survival in the treated patients was 60%, and median survival was 17.3 mo[33-35].

NUCLEIC ACID VACCINES

Nucleic acids have been well acknowledged as potent adjuvants[36,37]. Nucleic acid vaccines include plasmid DNA vaccines, RNA vaccines and viral vector vaccines. Both RNA and DNA have been utilized as adjuvants, meanwhile they take the responsibility to code for TAA[38]. RNA is transcribed *in vitro* (IVT) by a DNA template encoding the antigen and bacteriophage RNA polymerase; RNA vaccines can release a large number of tumor-derived specific antigens and induce humoral and cellular immune responses, provide costimulatory signals, and are well tolerated without carcinogenic potential[39,40].

VGX-3100

VGX-3100 is a DNA vaccine developed by INOVIO Pharmaceuticals, Inc. in the United States. The vaccine contains two DNA plasmids targeting E6 and E7 oncogenes associated with HPV-16 as well as HPV-18, which are responsible for transforming HPV-infected cells into precancerous lesions or cancer cells. Therefore, the vaccine is designed to increase the T cell immune response to eliminate infections caused by HPV-16 and HPV-18 and to destroy precancerous cells or lesions, without the associated risk of losing the patient's reproductive function[41,42].

Trimble *et al*[43] conducted a randomized, double-blind, placebo-controlled phase IIb clinical trial in patients with high-grade cervical squamous intraepithelial lesions (HSIL) related to HPV types 16 and 18, and 125 patients were divided into the VGX-3100 group; 42 patients were assigned to the placebo group. Results showed that 55 out of 114 patients in the VGX-3100 group (48.2%) and 12 out of 40 patients in the placebo group (30.0%) had histopathological regression [percentage difference between the two groups was 18.2% (95%CI: 1.3%-34.4%), P = 0.034)]. Patients in the treatment group were well tolerated, and the most common adverse reaction was erythema at the vaccination site, and no serious adverse events were reported.

The company launched the VGX-3100 critical phase III trial (REVEAL 1: NCT03185013) in June 2017 and completed the initial goal of recruiting 198 participants in June 2019. On March 1, 2021, INOVIO announced that the REVEAL 1 study has reached the primary and secondary clinical endpoints, thus being the first DNA medicine to achieve efficacy endpoints in a phase III trial. The REVEAL 1 study enrolled 201 patients with HPV-16/18-related HSIL. Among the 193 patients with evaluable efficacy, 23.7% (31/131) of the these in the treatment group reached the common primary endpoint of achieving histopathological regression of HSIL combined with virologic clearance of HPV-16 and/or HPV-18 at week 36, while the placebo group was 11.3% (7/62) and results were statistically significant (P = 0.022; 95%CI: 0.4-22.5). The study reached all secondary endpoints as well.

ProstAtak® (AdV-tk+valacyclovir, CAN-2409)

ProstAtak® is an adenovirus vector tumor vaccine developed by Advantagene, Inc. in the United States to prevent and treat recurrence of prostate cancer. It utilizes a gene transfer method to directly deliver a vaccine containing the herpes simplex virus thymidine kinase gene (aglatimagene besadenovec, AdV-tk) followed by an anti-herpetic prodrug valacyclovir into the prostate tumor *via* trans-rectal ultrasound guided injection, and then the patient continuously takes valacyclovir for 14 d. Theoretically, the initial local cytotoxicity is mediated by nucleoside analogues produced by valacyclovir phosphorylation, which activates the immune system by stimulating T-cell proliferation and IL-2 production therefore generates a systemic anti-tumor immune response. Advantagene Biotech launched a randomized, completely blind, placebo-controlled phase III clinical trial of ProstAtak® (PrTK03; NCT01436968) combined with radiotherapy in 711 patients with moderate to high-risk localized prostate cancer in September 2011. The subjects were randomly divided into treatment group and control group at a ratio of 2:1. The trial is expected to be initially completed in September 2023. Additionally, the company's phase II clinical trial of ProstAtak® (ULYSSES; NCT02768363) for patients with localized prostate cancer was also launched in May 2016. The trial has recruited 187 participants and its primary completion time was estimated to be March 2021.

FixVac (BNT111)

It has been well-acknowledged that mRNA has the potential to be promoted as an important character in therapeutic regimens since over 20 years ago. Since the successful development and current massive use of mRNA vaccines for coronavirus disease 2019 (COVID-19) immunization, more mRNA-based tumor immunotherapies have been under-developed. Some typical mRNA-based tumor vaccines and COVID-19 vaccines are listed in Tables 2 and 3. FixVac (BNT111) is an intravenously administered liposomal RNA (RNA-LPX) vaccine developed by Biopharmaceutical New Technologies (BioNTech), which comprises RNA-LPX encoding 4 TAAs—NY-ESO-1, melanoma-associated antigen A3, tyrosinase, and trans-membrane phosphatase with tensin homology[44]. These 4 antigens are non-mutated antigens quite common in melanoma and highly immunogenic but are barely expressed in normal tissues. The mRNA is enveloped by lipid nanoparticles to increase its stability, improve its transfection efficiency and avoid degradation[44,45]. With regard to the FixVac platform, its product candidates feature the proprietary immunogenic mRNA backbone optimized for encoding specific shared antigens; and RNA-lipoplex, or

Table 2 Typical mRNA-based tumor vaccines

Vaccine	mRNA-encoded antigen	Formulation type	Disease	NCT ID	Phases	Status	Sponsor/collaborator	Results
mRNA-2416	OX40L	LNP	Relapsed/Refractory Solid Tumor Malignancies or Lymphoma Ovarian Cancer	NCT03323398	Phase I/II	Recruiting	ModernaTX, Inc.	Any dose of intratumoral injection is tolerable when mRNA-2416 is administered alone. Results indicate increased OX40L protein expression, elevated PD-L1 levels and pro-inflammatory activity after mRNA-2416 injection
mRNA-2572	OX40L, IL-23, IL-36γ	LNP	Dose Escalation: Relapsed/Refractory Solid Tumor Malignancies or Lymphoma Dose Expansion: Triple Negative Breast Cancer, Head and Neck Squamous Cell Carcinoma, Non-Hodgkin Lymphoma, and Urothelial Cancer	NCT03739931	Phase I	Recruiting	ModernaTX, Inc., AstraZeneca	Any dose of intratumoral injection is tolerable when mRNA-2572 is administered alone or in combination with PD-L1 inhibitor. IFN-γ, TNF-α, and PD-L1 levels increased
mRNA-4157 KEYNOTE-603	Neo-Ag	LNP	Solid Tumors	NCT03313778	Phase I	Recruiting	ModernaTX, Inc., Merck Sharp & Dohme Corp.	All tested doses is tolerated, and clinical responses were observed when mRNA-4157 is combined with Pembrolizumab
KEYNOTE-942	Neo-Ag	LNP	Melanoma	NCT03897881	Phase II	Recruiting	ModernaTX, Inc., Merck Sharp & Dohme Corp.	Not available
mRNA-5671/Merck V941	KRAS mutations: G12D, G12V, G13D, G12C	LNP	NSCLC, Pancreatic cancer, Colorectal cancer	NCT03948763	Phase I	Recruiting	Merck Sharp & Dohme Corp.	Not available
FixVac (BNT111); Lipo-MERIT	NY-ESO-1, MAGEC3, tyrosinase, TPTE	Lipo-MERIT, LNP	Melanoma	NCT02410733	Phase I	Active, not recruiting	BioNTech SE	BNT111 alone or in combination with PD1, mediates durable objective responses in CPI-experienced patients with unresectable melanoma. Durable clinical responses in both monotherapy and combination with CPI are accompanied by the induction of strong CD4+ and CD8+ T cell immunity. BNT111 vaccination was safe and well tolerated with no dose limiting toxicity
RO7198457 (BNT122)	Neo-Ag	Lipo-MERIT, LNP	Melanoma, NSCLC, Bladder Cancer, CRC, Breast Cancer *etc*.	NCT03289962	Phase I	Recruiting	BioNTech, Genentech	The combination of RO7198457 and atezolizumab is generally well tolerated. RO7198457 combined with atezolizumab can induce pro-inflammatory cytokine release and peripheral T cell response in most patients
	Neo-Ag	Lipo-MERIT, LNP	Advanced Melanoma	NCT03815058	Phase II	Recruiting	Genentech, Inc., BioNTech SE	Not available
	Neo-Ag	Lipo-MERIT, LNP	Stage II and III CRC (surgically resected)	NCT04486378	Phase II	Recruiting	BioNTech SE	Not available
	Neo-Ag	Lipo-MERIT, LNP	Pancreatic Cancer (surgically resected)	NCT04161755	Phase I	Recruiting	Memorial Sloan Kettering Cancer Center, Genentech, Inc.	Not available

	Neo-Ag	Lipo-MERIT, LNP	NSCLC	NCT04267237	Phase II	Withdrawn	Hoffmann-La Roche	Not available
SAR441000 (BNT131)	IL-12sc, IL-15sushi, IFNα and GM-CSF	Various formulations	advanced melanoma	NCT03871348	Phase I	Recruiting	Sanofi, BioNTech RNA Pharmaceuticals GmbH	Not available
RiboMab (BNT141)	mRNA encoding secreted IgG antibodies that target multiple epithelial solid tumors	Various liver-targeting LNP formulations	CLDN18.2-positive Solid Tumors	NCT04683939	Phase I/II	Not yet recruiting	BioNTech SE	Not available
IVAC MUTANOME, RBL001/RBL002	Neo-Ag/TAA	naked mRNA	Advanced Melanoma	NCT02035956	Phase I	Completed	BioNTech RNA Pharmaceuticals GmbH, BioNTech SE	
CV8102	TLR7/8/RIG-1 agonist based on noncoding single stranded RNA	RNActive, (Protamine)	Melanoma (Skin), Squamous Cell Carcinoma of the Skin Carcinoma, Squamous Cell of Head and Neck Carcinoma, Adenoid Cystic	NCT03291002	Phase I	Recruiting	CureVac AG, Syneos Health	Not available
	Peptide vaccine and mRNA	IMA970A plus CV8102 and Cyclophosphamide	Hepatocellular carcinoma	NCT03203005	Phase I/II	Completed	National Cancer Institute, Naples, immatics Biotechnologies GmbH, CureVac AG, European Commission-FP7-Health-2013-Innovation-1	Not available
BI-1361849 (CV9202)	NY-ESO-1, MAGE-C2, MAGE-C1, survivin, 5 T4, MUC1	RNActive, Protamine	Metastatic NSCLC	NCT03164772	Phase I/II	Active, not recruiting	Ludwig Institute for Cancer Research, Cancer Research Institute, New York City; Boehringer Ingelheim, MedImmune LLC, CureVac AG, PharmaJet, Inc.	CV9202 was well-tolerated, and antigen specific immune responses were detected in majority of patients (84%)
CV9201	MAGE-C1, MAGE-C2, NY-SEO-1, survivin,5 T4	RNActive, Protamine	Stage IIIB/IV NSCLC	NCT00923312	Phase I/II	Completed	CureVac AG	CV9201 was well-tolerated and results indicated immune responses after vaccination. Median PFS and OS were 5 and 10.8 mo, respectively
CV9103	PSA, PSCA, PSMA, STEAP1	RNActive, Protamine	Prostate cancer	NCT00831467	Phase I/II	Completed	CureVac AG	CV9103 is well tolerated and immunogenic
CV9104	PSA, PSCA, PSMA, STEAP1, PAP, MUC1	RNActive, Protamine	Prostate cancer	NCT01817738	Phase I/II	Terminated	CureVac AG	Terminated due to insufficient activities

LNP: Lipid Nanoparticle; Neo-Ag: Neoantigen; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor-α; PD-L1: Programmed death-ligand 1; IL: Interleukin; GM-CSF: Granulocyte-macrophage colony stimulating factor; NSCLC: Non-small cell lung cancer.

RNA-LPX, the delivery formulation, meant to enhance mRNA's stability and translation, targeting DCs in lymphoid compartments body-wide and to stimulate potent immune responses[44,46]. BNT111 is an off-the-shelf mRNA vaccine product from the FixVac platform and not individualized for particular patients, but its proprietary RNA-LPX formulation with the general utility of these 4 non-mutant

Table 3 Typical mRNA-based coronavirus disease 2019 vaccines have entered phase III or IV clinical trials

Vaccine	NCT ID	Title	Phase	Status	Estimated number of participants	Sponsor/collaborator
BNT162b2	NCT04816669	Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Lyophilized Formulation of BNT162b2 Against COVID-19 in Healthy Adults	Phase III	Recruiting	550	BioNTech SE, Pfizer
	NCT04713553	A Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Production Lots and Dose Levels of BNT162b2 Against COVID-19 in Healthy Participants	Phase III	Recruiting	1530	BioNTech SE, Pfizer
	NCT04754594	Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS-CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older	Phase II/III	Recruiting	4000	BioNTech SE, Pfizer
	NCT04775069	Antibody Response to COVID-19 Vaccines in Liver Disease Patients	Phase IV	Not yet recruiting	900	Humanity & Health Medical Group Limited
mRNA-1273	NCT04860297	A Study to Evaluate Safety and Immunogenicity of mRNA-1273 Vaccine to Prevent COVID-19 in Adult Organ Transplant Recipients and in Healthy Adult Participants	Phase III	Recruiting	240	ModernaTX, Inc.
	NCT04796896	A Study to Evaluate Safety and Effectiveness of mRNA-1273 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age	Phase II/III	Recruiting	6750	ModernaTX, Inc.
	NCT04470427	A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19	Phase III	Active, not recruiting	30420	ModernaTX, Inc., Biomedical Advanced Research and Development Authority, National Institute of Allergy and Infectious Diseases (NIAID)
	NCT04649151	A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19	Phase II/III	Active, not recruiting	3000	ModernaTX, Inc., Biomedical Advanced Research and Development Authority
CV-NCOV-011	NCT04848467	A Trial Studying the SARS-CoV-2 mRNA Vaccine CVnCoV to Learn About the Immune Response, the Safety, and the Degree of Typical Vaccination Reactions When CVnCoV is Given at the Same Time as a Flu Vaccine Compared to When the Vaccines Are Separately Given in Adults 60 Years of Age and Older (CV-NCOV-011)	Phase III	Not yet recruiting	1000	Bayer, CureVac AG
CVnCoV	NCT04860258	A Study to Evaluate Safety, Reactogenicity and Immunogenicity of the SARS-CoV-2 mRNA Vaccine CVnCoV in Adults With Co-morbidities for COVID-19	Phase III	Not yet recruiting	1200	CureVac AG
	NCT04838847	A Study to Evaluate the Immunogenicity and Safety of the SARS-CoV-2 mRNA Vaccine CVnCoV in Elderly Adults Compared to Younger Adults for COVID-19	Phase III	Not yet recruiting	180	CureVac AG
	NCT04652102	A Study to Determine the Safety and Efficacy of SARS-CoV-2 mRNA Vaccine CVnCoV in Adults for COVID-19	Phase II/III	Recruiting	36500	CureVac AG
	NCT04674189	A Study to Evaluate the Safety and Immunogenicity of Vaccine CVnCoV in Healthy Adults in Germany for COVID-19	Phase III	Recruiting	2520	CureVac AG
SARS-CoV-2 mRNA Vaccine	NCT04847102	A Phase III Clinical Study of a SARS-CoV-2 Messenger Ribonucleic Acid (mRNA) Vaccine Candidate Against COVID-19 in Population Aged 18 Years and Above	Phase III	Not yet recruiting	28000	Walvax Biotechnology Co., Ltd., Abogen Biosciences Co. Ltd., Yuxi Walvax Biotechnology Co., Ltd.,
CoVPN 3006	NCT04811664	A Study of SARS CoV-2 Infection and Potential Transmission in University Students Immunized With Moderna COVID-19 Vaccine (CoVPN 3006)	Phase III	Recruiting	37500	National Institute of Allergy and Infectious Diseases (NIAID)

KYRIOS	NCT04869358	Exploring the Immune Response to SARS-CoV-2/COVID-19 Vaccines in Patients With Relapsing Multiple Sclerosis (RMS) Treated With Ofatumumab (KYRIOS)	Phase IV	Not yet recruiting	40	
ENFORCE	NCT04760132	National Cohort Study of Effectiveness and Safety of SARS-CoV-2/COVID-19 Vaccines (ENFORCE) (ENFORCE)	Phase IV	Recruiting	10000	Jens D Lundgren, MD, Ministry of the Interior and Health, Denmark; Rigshospitalet, Denmark
AMA-VACC	NCT04792567	Exploring the Immune Response to SARS-CoV-2 modRNA Vaccines in Patients With Secondary Progressive Multiple Sclerosis (AMA-VACC) (AMA-VACC)	Phase IV	Recruiting	60	
COVAXID	NCT04780659	COVID-19 Vaccination of Immunodeficient Persons (COVAXID) (COVAXID)	Phase IV	Recruiting	540	Karolinska University Hospital, Karolinska Institutet
DemiVac	NCT04852861	Safety and Immunogenicity of Demi-dose of Two Covid-19 mRNA Vaccines in Healthy Population (DemiVac)	Phase IV	Not yet recruiting	200	Sciensano, Mensura EDPB, Institute of Tropical Medicine, Belgium; Erasme University Hospital

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

shared tumor antigens turned out to be effective.

Sahin *et al*[47] has conducted the clinical trial named Lipo-MERIT (NCT02410733), which is a multicenter, open-label, dose-escalation phase 1 trial to evaluate the safety and tolerability of vaccinated patients with stage IIIB-C and stage IV melanoma. According to the interim analysis as of July 29, 2019 of 89 patients who was intravenously administered BNT111 ranging from 7.2 μg to 400 μg, BNT111 alone or in combination with blockade of the CPI PD1, mediates durable objective responses in CPI-experienced patients with unresectable melanoma. Durable clinical responses in both monotherapy and combinatory therapy were accompanied by the induction of strong $CD4^+$ and $CD8^+$ T cell immunity. BNT111 vaccination was safe and well tolerated with no dose limiting toxicity. Most common adverse events were mild to moderate, transient flu-like symptoms, such as pyrexia and chills. Mostly they are early-onset, transient and manageable with antipyretics, and could be resolved within 24 h.

Based on the promising results of Lipo-MERIT, BioNTech launched the randomized, multi-site, phase II trial (NCT04526899) designed to evaluate the efficacy, tolerability, and safety of BNT111 combined with cemiplimab (Libtayo®) in anti-PD1-refractory/relapsed patients with unresectable Stage III or IV melanoma. The trial was scheduled to recruit 120 participants and estimated to start in May 2021[48]. In addition, iNeST is another typical platform in BioNTech and represents the pioneer in developing fully individualized cancer immunotherapies, which utilizes optimized mRNA encoding neoantigens identified on particular patients and features proprietary size- and charge-based RNA-LPX targeting DCs formulation[44]. There are four ongoing clinical trials based on its product candidate RO7198457 (BNT122), two of which has entered phase 2.

CONCLUSION

The pursuit of tumor vaccines has been for more than a century. In the field of immunotherapy, the past decade has witnessed tremendous progress in the usage of immune checkpoint blockades and the adoptive cell therapy, although still many patients fail to benefit from the immune therapies alone. Such effectiveness of novel immune therapies has greatly motivated people to revisit the concept of tumor vaccines. At present, one of the main restricting factors of tumor vaccines is the weak immunogenicity of the tumor antigens, which poses tumor immune tolerance or immune escape. Moreover, since the tumors in patients are highly heterogeneous, the development of tumor vaccines is undergoing a transition from universality to individualization, so that the treatment is more tailored to individual patient. Different types of vaccines have their own distinct advantages and disadvantages. Tumor cell vaccine contains the full spectrum of tumor antigens and it is simple to prepare. However, it requires a large amount of autologous tumor tissues or allogeneic tumor cell lines, and their immunogenicity is usually weak. DC vaccine can stimulate a wide range of immune responses and can be loaded with antigens in diverse ways, but DC

cell culture *in vitro* is challenging, and the vaccine preparation process may generate immature DCs which may induce immune tolerance. Peptide vaccine has strong specificity and high safety, and is not restricted by MHC haplotype and easy to modify, but it tends to provoke a weak immune response and is prone to tumor antigen modulation. With regard to the nucleic acid vaccine, it is easy to produce, economical and safe, and can elicit a wide range of immune responses, but it requires to be used in a large amount so that it can be taken up by cells in sufficient amount to stimulate effective immunity. It is also worth noting that storage, stability and delivery techniques of nucleic acid vaccine are also issues to be overcome.

The past 20 years have witnessed the application of mRNA technology in multiple indications and its transition from theory to vaccine products and clinical treatments. Before the global health pandemic COVID-19, mRNA technology had already been regarded as the most advanced in the area of cancer immunotherapy but its full potential remains latent. The efforts made to the recent fast approval of two mRNA-based COVID-19 vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech), definitely promotes the mRNA vaccine development in every aspect, such as its modification strategy to stabilize and to control its immunogenicity, cell delivery strategy and transportation and maintenance strategy. Undoubtedly, this will be a huge push to apply mRNA technology in additional infectious disease prevention and in the area of cancer treatment. We envision mRNA technology is poised to be the next generation cancer immunotherapy in the near future.

In summary, we are experiencing an outbreak of different types of tumor vaccines, and we are making every effort to transform the idea of therapeutic tumor vaccines into a standard clinical application. Many pending questions remain to be addressed. However, with the advancement of new technologies and deepened understanding of tumor immunology, the joint efforts of scientific researchers from all over the world will certainly make the development of therapeutic tumor vaccines a good prospect.

REFERENCES

1 **Slaney CY**, Kershaw MH. Challenges and Opportunities for Effective Cancer Immunotherapies. *Cancers (Basel)* 2020; **12** [PMID: 33126513 DOI: 10.3390/cancers12113164]

2 **Guo C**, Manjili MH, Subjeck JR, Sarkar D, Fisher PB, Wang XY. Therapeutic cancer vaccines: past, present, and future. *Adv Cancer Res* 2013; **119**: 421-475 [PMID: 23870514 DOI: 10.1016/B978-0-12-407190-2.00007-1]

3 **Wong KK**, Li WA, Mooney DJ, Dranoff G. Advances in Therapeutic Cancer Vaccines. *Adv Immunol* 2016; **130**: 191-249 [PMID: 26923002 DOI: 10.1016/bs.ai.2015.12.001]

4 **Dores GM**, Bryant-Genevier M, Perez-Vilar S. Adverse Events Associated With the Use of Sipuleucel-T Reported to the US Food and Drug Administration's Adverse Event Reporting System, 2010-2017. *JAMA Netw Open* 2019; **2**: e199249 [PMID: 31411714 DOI: 10.1001/jamanetworkopen.2019.9249]

5 **Andtbacka RH**, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, Delman KA, Spitler LE, Puzanov I, Agarwala SS, Milhem M, Cranmer L, Curti B, Lewis K, Ross M, Guthrie T, Linette GP, Daniels GA, Harrington K, Middleton MR, Miller WH Jr, Zager JS, Ye Y, Yao B, Li A, Doleman S, VanderWalde A, Gansert J, Coffin RS. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *J Clin Oncol* 2015; **33**: 2780-2788 [PMID: 26014293 DOI: 10.1200/JCO.2014.58.3377]

6 **Ogi C**, Aruga A. Clinical evaluation of therapeutic cancer vaccines. *Hum Vaccin Immunother* 2013; **9**: 1049-1057 [PMID: 23454867 DOI: 10.4161/hv.23917]

7 **Sprooten J**, Ceusters J, Coosemans A, Agostinis P, De Vleeschouwer S, Zitvogel L, Kroemer G, Galluzzi L, Garg AD. Trial watch: dendritic cell vaccination for cancer immunotherapy. *Oncoimmunology* 2019; **8**: e1638212 [PMID: 31646087 DOI: 10.1080/2162402X.2019.1638212]

8 **Roy S**, Sethi TK, Taylor D, Kim YJ, Johnson DB. Breakthrough concepts in immune-oncology: Cancer vaccines at the bedside. *J Leukoc Biol* 2020; **108**: 1455-1489 [PMID: 32557857 DOI: 10.1002/JLB.5BT0420-585RR]

9 **Vermorken JB**, Claessen AM, van Tinteren H, Gall HE, Ezinga R, Meijer S, Scheper RJ, Meijer CJ, Bloemena E, Ransom JH, Hanna MG Jr, Pinedo HM. Active specific immunotherapy for stage II and stage III human colon cancer: a randomised trial. *Lancet* 1999; **353**: 345-350 [PMID: 9950438 DOI: 10.1016/S0140-6736(98)07186-4]

10 **OncoVAX® Phase IIIa Study (8701) Results in Stage II Colon Cancer**. OncoVAX® Cancer Vaccine Clinical Results - Vaccinogen (vaccinogen-oncovax.com). [cited 5 May 2021]. Available from: https://vaccinogen-oncovax.com/oncovax/clinical-results/

11 **Michael G**. Vaccine Therapy in Treating Patients With Stage II or Stage III Colon Cancer That Has Been Removed During Surgery. In: ClinicalTrials.gov [Internet]. National Cancer Institute (NCI): U.S. National Library of Medicine. [cited 5 May 2021]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00016133

12 **Senzer N**, Barve M, Kuhn J, Melnyk A, Beitsch P, Lazar M, Lifshitz S, Magee M, Oh J, Mill SW, Bedell C, Higgs C, Kumar P, Yu Y, Norvell F, Phalon C, Taquet N, Rao DD, Wang Z, Jay CM, Pappen BO, Wallraven G, Brunicardi FC, Shanahan DM, Maples PB, Nemunaitis J. Phase I trial of "bi-shRNAi(furin)/GMCSF DNA/autologous tumor cell" vaccine (FANG) in advanced cancer. *Mol Ther* 2012; **20**: 679-686 [PMID: 22186789 DOI: 10.1038/mt.2011.269]

13 **Nemunaitis J**, Barve M, Orr D, Kuhn J, Magee M, Lamont J, Bedell C, Wallraven G, Pappen BO, Roth A, Horvath S, Nemunaitis D, Kumar P, Maples PB, Senzer N. Summary of bi-shRNA/GM-CSF augmented autologous tumor cell immunotherapy (FANG™) in advanced cancer of the liver. *Oncology* 2014; **87**: 21-29 [PMID: 24968881 DOI: 10.1159/000360993]

14 **Oh J**, Barve M, Matthews CM, Koon EC, Heffernan TP, Fine B, Grosen E, Bergman MK, Fleming EL, DeMars LR, West L, Spitz DL, Goodman H, Hancock KC, Wallraven G, Kumar P, Bognar E, Manning L, Pappen BO, Adams N, Senzer N, Nemunaitis J. Phase II study of Vigil® DNA engineered immunotherapy as maintenance in advanced stage ovarian cancer. *Gynecol Oncol* 2016; **143**: 504-510 [PMID: 27678295 DOI: 10.1016/j.ygyno.2016.09.018]

15 **Rocconi RP**, Grosen EA, Ghamande SA, Chan JK, Barve MA, Oh J, Tewari D, Morris PC, Stevens EE, Bottsford-Miller JN, Tang M, Aaron P, Stanbery L, Horvath S, Wallraven G, Bognar E, Manning L, Nemunaitis J, Shanahan D, Slomovitz BM, Herzog TJ, Monk BJ, Coleman RL. Gemogenovatucel-T (Vigil) immunotherapy as maintenance in frontline stage III/IV ovarian cancer (VITAL): a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Oncol* 2020; **21**: 1661-1672 [PMID: 33271095 DOI: 10.1016/S1470-2045(20)30533-7]

16 **Rocconi RP**, Monk BJ, Walter A, Herzog TJ, Galanis E, Manning L, Bognar E, Wallraven G, Stanbery L, Aaron P, Senzer N, Coleman RL, Nemunaitis J. Gemogenovatucel-T (Vigil) immunotherapy demonstrates clinical benefit in homologous recombination proficient (HRP) ovarian cancer. *Gynecol Oncol* 2021; **161**: 676-680 [PMID: 33715892 DOI: 10.1016/j.ygyno.2021.03.009]

17 **Kalinski P**, Okada H. Polarized dendritic cells as cancer vaccines: directing effector-type T cells to tumors. *Semin Immunol* 2010; **22**: 173-182 [PMID: 20409732 DOI: 10.1016/j.smim.2010.03.002]

18 **Steinman RM**. Decisions about dendritic cells: past, present, and future. *Annu Rev Immunol* 2012; **30**: 1-22 [PMID: 22136168 DOI: 10.1146/annurev-immunol-100311-102839]

19 **Barth RJ Jr**, Fisher DA, Wallace PK, Channon JY, Noelle RJ, Gui J, Ernstoff MS. A randomized trial of *ex vivo* CD40L activation of a dendritic cell vaccine in colorectal cancer patients: tumor-specific immune responses are associated with improved survival. *Clin Cancer Res* 2010; **16**: 5548-5556 [PMID: 20884622 DOI: 10.1158/1078-0432.CCR-10-2138]

20 **Lesterhuis WJ**, de Vries IJ, Schreibelt G, Lambeck AJ, Aarntzen EH, Jacobs JF, Scharenborg NM, van de Rakt MW, de Boer AJ, Croockewit S, van Rossum MM, Mus R, Oyen WJ, Boerman OC, Lucas S, Adema GJ, Punt CJ, Figdor CG. Route of administration modulates the induction of dendritic cell vaccine-induced antigen-specific T cells in advanced melanoma patients. *Clin Cancer Res* 2011; **17**: 5725-5735 [PMID: 21771874 DOI: 10.1158/1078-0432.CCR-11-1261]

21 **Podrazil M**, Horvath R, Becht E, Rozkova D, Bilkova P, Sochorova K, Hromadkova H, Kayserova J, Vavrova K, Lastovicka J, Vrabcova P, Kubackova K, Gasova Z, Jarolim L, Babjuk M, Spisek R, Bartunkova J, Fucikova J. Phase I/II clinical trial of dendritic-cell based immunotherapy (DCVAC/PCa) combined with chemotherapy in patients with metastatic, castration-resistant prostate cancer. *Oncotarget* 2015; **6**: 18192-18205 [PMID: 26078335 DOI: 10.18632/oncotarget.4145]

22 **Fucikova J**, Podrazil M, Jarolim L, Bilkova P, Hensler M, Becht E, Gasova Z, Klouckova J, Kayserova J, Horvath R, Fialova A, Vavrova K, Sochorova K, Rozkova D, Spisek R, Bartunkova J. Phase I/II trial of dendritic cell-based active cellular immunotherapy with DCVAC/PCa in patients with rising PSA after primary prostatectomy or salvage radiotherapy for the treatment of prostate cancer. *Cancer Immunol Immunother* 2018; **67**: 89-100 [PMID: 28948333 DOI: 10.1007/s00262-017-2068-x]

23 **Amin A**, Dudek AZ, Logan TF, Lance RS, Holzbeierlein JM, Knox JJ, Master VA, Pal SK, Miller WH Jr, Karsh LI, Tcherepanova IY, DeBenedette MA, Williams WL, Plessinger DC, Nicolette CA, Figlin RA. Survival with AGS-003, an autologous dendritic cell-based immunotherapy, in combination with sunitinib in unfavorable risk patients with advanced renal cell carcinoma (RCC): Phase 2 study results. *J Immunother Cancer* 2015; **3**: 14 [PMID: 25901286 DOI: 10.1186/s40425-015-0055-3]

24 **Figlin RA**, Tannir NM, Uzzo RG, Tykodi SS, Chen DYT, Master V, Kapoor A, Vaena D, Lowrance W, Bratslavsky G, DeBenedette M, Gamble A, Plachco A, Norris MS, Horvatinovich J, Tcherepanova IY, Nicolette CA, Wood CG; ADAPT study group. Results of the ADAPT Phase 3 Study of Rocapuldencel-T in Combination with Sunitinib as First-Line Therapy in Patients with Metastatic Renal Cell Carcinoma. *Clin Cancer Res* 2020; **26**: 2327-2336 [PMID: 32034074 DOI: 10.1158/1078-0432.CCR-19-2427]

25 **DCVax ® Technology**. Northwest Biotherapeutics. [cited 5 May 2021]. Available from: https://nwbio.com/dcvax-technology/

26 **Hdeib A**, Sloan AE. Dendritic cell immunotherapy for solid tumors: evaluation of the DCVax® platform in the treatment of glioblastoma multiforme. *CNS Oncol* 2015; **4**: 63-69 [PMID: 25768330 DOI: 10.2217/cns.14.54]

27 **Liau LM**, Ashkan K, Tran DD, Campian JL, Trusheim JE, Cobbs CS, Heth JA, Salacz M, Taylor S, D'Andre SD, Iwamoto FM, Dropcho EJ, Moshel YA, Walter KA, Pillainayagam CP, Aiken R, Chaudhary R, Goldlust SA, Bota DA, Duic P, Grewal J, Elinzano H, Toms SA, Lillehei KO, Mikkelsen T, Walbert T, Abram SR, Brenner AJ, Brem S, Ewend MG, Khagi S, Portnow J, Kim LJ,

Loudon WG, Thompson RC, Avigan DE, Fink KL, Geoffroy FJ, Lindhorst S, Lutzky J, Sloan AE, Schackert G, Krex D, Meisel HJ, Wu J, Davis RP, Duma C, Etame AB, Mathieu D, Kesari S, Piccioni D, Westphal M, Baskin DS, New PZ, Lacroix M, May SA, Pluard TJ, Tse V, Green RM, Villano JL, Pearlman M, Petrecca K, Schulder M, Taylor LP, Maida AE, Prins RM, Cloughesy TF, Mulholland P, Bosch ML. First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. *J Transl Med* 2018; **16**: 142 [PMID: 29843811 DOI: 10.1186/s12967-018-1507-6]

28 **van der Bruggen P**, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, Boon T. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. *Science* 1991; **254**: 1643-1647 [PMID: 1840703 DOI: 10.1126/science.1840703]

29 **Kallen KJ**, Gnad-Vogt U, Scheel B, Rippin G, Stenzl A. A phase I/IIa study of the mRNA based cancer vaccine CV9103 prepared with the RNActive technology results in distinctly longer survival than predicted by the Halabi Nomogram which correlates with the induction of antigen-specific immune responses. *J Immunother Cancer* 2013; **1**: P219 [DOI: 10.1186/2051-1426-1-S1-P219]

30 **Craig S**. Study of a Melanoma Vaccine in Stage IIb, IIc, and III Melanoma Patients (MAVIS). In: ClinicalTrials.gov [Internet]. Polynoma LLC: U.S. National Library of Medicine. [cited 6 May 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT01546571

31 **Tedopi®**. OSE Immunotherapeutics. [cited 6 May 2021]. Available from: https://ose-immuno.com/en/ose-product/tedopi/

32 **Santiago V**. Early signs of activity of Tedopi (OSE2101), a multiple neoepitope vaccine, in a phase 3 trial in advanced lung cancer patients after failure to previous immune checkpoint inhibitors (ICI) Atalante -1 study trial. AACR 2019. [cited 6 May 2021]. Available from: https://ose-immuno.com/wp-content/uploads/2019/04/Viteri-Early-sings-Tedopi-Final-1.pdf

33 **Beebe M**, Qin M, Moi M, Wu S, Heiati H, Walker L, Newman M, Fikes J, Ishioka GY. Formulation and characterization of a ten-peptide single-vial vaccine, EP-2101, designed to induce cytotoxic T-lymphocyte responses for cancer immunotherapy. *Hum Vaccin* 2008; **4**: 210-218 [PMID: 18382135 DOI: 10.4161/hv.4.3.5291]

34 **Nemunaitis J**, Cunningham C, Bender J, Ishioka G, Maples P, Pappen B, Stephenson J, Morse M, Mills B, Greco A, McCune D, Steis R, Nugent F, Khong HT, Richards D. Phase II trial of a 10-epitope CTL vaccine, IDM-2101, in metastatic NSCLC patients: Induction of immune responses and clinical efficacy. *J Clin Oncol* 2007; **25**: 3068-3068 [DOI: 10.1200/jco.2007.25.18_suppl.3068]

35 **Barve M**, Bender J, Senzer N, Cunningham C, Greco FA, McCune D, Steis R, Khong H, Richards D, Stephenson J, Ganesa P, Nemunaitis J, Ishioka G, Pappen B, Nemunaitis M, Morse M, Mills B, Maples PB, Sherman J, Nemunaitis JJ. Induction of immune responses and clinical efficacy in a phase II trial of IDM-2101, a 10-epitope cytotoxic T-lymphocyte vaccine, in metastatic non-small-cell lung cancer. *J Clin Oncol* 2008; **26**: 4418-4425 [PMID: 18802154 DOI: 10.1200/JCO.2008.16.6462]

36 **Restifo NP**, Ying H, Hwang L, Leitner WW. The promise of nucleic acid vaccines. *Gene Ther* 2000; **7**: 89-92 [PMID: 10673713 DOI: 10.1038/sj.gt.3301117]

37 **Hobernik D**, Bros M. DNA Vaccines-How Far From Clinical Use? *Int J Mol Sci* 2018; **19** [PMID: 30445702 DOI: 10.3390/ijms19113605]

38 **Ulmer JB**, Mason PW, Geall A, Mandl CW. RNA-based vaccines. *Vaccine* 2012; **30**: 4414-4418 [PMID: 22546329 DOI: 10.1016/j.vaccine.2012.04.060]

39 **Pardi N**, Muramatsu H, Weissman D, Karikó K. In vitro transcription of long RNA containing modified nucleosides. *Methods Mol Biol* 2013; **969**: 29-42 [PMID: 23296925 DOI: 10.1007/978-1-62703-260-5_2]

40 **McNamara MA**, Nair SK, Holl EK. RNA-Based Vaccines in Cancer Immunotherapy. *J Immunol Res* 2015; **2015**: 794528 [PMID: 26665011 DOI: 10.1155/2015/794528]

41 **Morrow MP**, Kraynyak KA, Sylvester AJ, Dallas M, Knoblock D, Boyer JD, Yan J, Vang R, Khan AS, Humeau L, Sardesai NY, Kim JJ, Plotkin S, Weiner DB, Trimble CL, Bagarazzi ML. Clinical and Immunologic Biomarkers for Histologic Regression of High-Grade Cervical Dysplasia and Clearance of HPV16 and HPV18 after Immunotherapy. *Clin Cancer Res* 2018; **24**: 276-294 [PMID: 29084917 DOI: 10.1158/1078-0432.CCR-17-2335]

42 **Bagarazzi ML**, Yan J, Morrow MP, Shen X, Parker RL, Lee JC, Giffear M, Pankhong P, Khan AS, Broderick KE, Knott C, Lin F, Boyer JD, Draghia-Akli R, White CJ, Kim JJ, Weiner DB, Sardesai NY. Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012; **4**: 155ra138 [PMID: 23052295 DOI: 10.1126/scitranslmed.3004414]

43 **Trimble CL**, Morrow MP, Kraynyak KA, Shen X, Dallas M, Yan J, Edwards L, Parker RL, Denny L, Giffear M, Brown AS, Marcozzi-Pierce K, Shah D, Slager AM, Sylvester AJ, Khan A, Broderick KE, Juba RJ, Herring TA, Boyer J, Lee J, Sardesai NY, Weiner DB, Bagarazzi ML. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet* 2015; **386**: 2078-2088 [PMID: 26386540 DOI: 10.1016/S0140-6736(15)00239-1]

44 **BIONTECH**. BioNTech Publishes Data from mRNA-based BNT111 FixVac Melanoma Trial in Nature. [cited 6 May 2021]. Available from: https://investors.biontech.de/news-releases/news-release-details/biontech-publishes-data-mrna-based-bnt111-fixvac-melanoma-trial/

45 **Miao L**, Zhang Y, Huang L. mRNA vaccine for cancer immunotherapy. *Mol Cancer* 2021; **20**: 41 [PMID: 33632261 DOI: 10.1186/s12943-021-01335-5]

46 **Hollingsworth RE**, Jansen K. Turning the corner on therapeutic cancer vaccines. *NPJ Vaccines* 2019;

4: 7 [PMID: 30774998 DOI: 10.1038/s41541-019-0103-y]

47 **Sahin U**, Oehm P, Derhovanessian E, Jabulowsky RA, Vormehr M, Gold M, Maurus D, Schwarck-Kokarakis D, Kuhn AN, Omokoko T, Kranz LM, Diken M, Kreiter S, Haas H, Attig S, Rae R, Cuk K, Kemmer-Brück A, Breitkreuz A, Tolliver C, Caspar J, Quinkhardt J, Hebich L, Stein M, Hohberger A, Vogler I, Liebig I, Renken S, Sikorski J, Leierer M, Müller V, Mitzel-Rink H, Miederer M, Huber C, Grabbe S, Utikal J, Pinter A, Kaufmann R, Hassel JC, Loquai C, Türeci Ö. An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma. *Nature* 2020; **585**: 107-112 [PMID: 32728218 DOI: 10.1038/s41586-020-2537-9]

48 **Agents in Patients With Anti-PD1-refractory/Relapsed**. Unresectable Stage III or IV Melanoma. In: ClinicalTrials.gov [Internet]. BioNTech SE: U.S. National Library of Medicine. [cited 25 April 2015]. Available from: https://clinicaltrials.gov/ct2/show/NCT04526899?cond=NCT04526899&draw=2&rank=1

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MINIREVIEWS

Application of retroperitoneal laparoscopy and robotic surgery in complex adrenal tumors

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Abstract

As a surgical method for the treatment of adrenal surgical diseases, laparoscopy has the advantages of small trauma, short operation time, less bleeding, and fast postoperative recovery. It is considered as the gold standard for the treatment of adrenal surgical diseases. Retroperitoneal laparoscopy is widely used because it does not pass through the abdominal cavity, does not interfere with internal organs, and has little effect on gastrointestinal function. However, complex adrenal tumors have the characteristics of large volume, compression of adjacent tissues, and invasion of surrounding tissues, so they are rarely treated by retroperitoneal laparoscopy. In recent years, with the development of laparoscopic technology and the progress of surgical technology, robotic surgery has been gradually applied to the surgical treatment of complex adrenal tumors. This paper reviews the clinical application of retroperitoneal laparoscopic surgery and robotic surgery in the treatment of complex adrenal tumors.

Key Words: Retroperitoneal laparoscopic; Robotic surgical procedures; Complex adrenal tumors; Clinical application; Robotic

Core Tip: The posterior laparoscopy does not interfere with the internal organs and has little effect on the function of the gastrointestinal tract, thus widely being used. However, complex adrenal tumors are characterized by large volume, compression of adjacent tissues, and invasion of surrounding tissues. Therefore, they are rarely treated by retroperitoneal laparoscopic surgery. Recently, with the development of laparoscopic techniques and advances in surgical techniques, reports about retroperitoneal laparoscopic adrenalectomy have gradually increased. This article reviews the clinical application of laparoscopy in complex adrenal tumors.

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INTRODUCTION

Adrenal tumors are one of the most common tumors in the urinary system, and surgery is the main method of treatment. Gagner *et al*[1] first reported transabdominal laparoscopic surgery for Cushing syndrome. With the progress of laparoscopic surgery technology and the improvement of equipment, laparoscopic surgery for adrenal diseases has been widely used by urologists. Because of the small space of the retroperitoneum, laparoscopic surgery for the treatment of complex adrenal tumors requires a highly skilled technique. There are few reports regarding retroperitoneal laparoscopic surgery for complex adrenal tumors. Recently, there are more and more reports on robot assisted laparoscopic technology. The Da Vinci surgical robot system provides articulated instruments, three-dimensional (3D) vision, tremor filtering, and stable cameras. It can make up for the defects of traditional laparoscopy.

RETROPERITONEAL LAPAROSCOPY IN ADRENAL TUMORS

In 1992, Gagner *et al*[1] first reported laparoscopic adrenalectomy. Compared with open surgery, laparoscopic adrenalectomy has the advantages of less bleeding, less trauma, faster recovery, and fewer intraoperative and postoperative complications, and soon has been promoted and applied all over the world. Retroperitoneal laparoscopy was first reported by Walz *et al*[2] in 1996. This technology became popular because it can directly and quickly expose the adrenal gland without going through the peritoneal cavity, and does not need to dissect the intraperitoneal structures. In the same year, Mercan *et al*[3] performed eight cases of adrenalectomy and the average operation time was about 150 min. In 2011, Shi *et al*[4] elaborated the surgical methods and skills of anatomical retroperitoneal laparoscopic adrenalectomy. In recent years, with the development of endoscopic technology, robot assisted retroperitoneal laparoscopic technology is gradually increasing. Robot surgery system has the advantages of clear operation field, flexible operation, and fine action and is gradually welcomed[5].

ANATOMIC PATHWAY AND OPERATIVE TECHNIQUE OF RETROPERITONEAL LAPAROSCOPY

However, there are disputes about complex adrenal tumors. It has been found that retroperitoneal laparoscopic anatomical three-layer method has the advantages of less blood loss and shorter operation time in surgery for huge adrenal masses[6].

During the retroperitoneal laparoscopical surgery, the patient usually lies on the healthy side. First, the skin is cut at 1.5 cm above the iliac crest of the midaxillary line, the subcutaneous tissue and fat are separated by fingers, and then an artificial balloon is inserted into the retroperitoneum. After being filled with 500 mL of gas for about 5 min, the balloon is withdrawn, and trocars are inserted for laparoscopy under monitor. After entering the retroperitoneal cavity, the location of Gerota's extrafascial cavity is identified, and the adipose tissue outside the Gerota's fascia and peritoneum is sharply separated from the inferior edge of diaphragm to the iliac fossa with an ultrasonic scalpel.

At the first level, the relatively avascular space between the perirenal fat sac above the medial side of the kidney and the anterior layer of Gerota fascia is separated to find the adrenal tumor and expose its anterior surface. At the second level, the relatively avascular space between the perirenal fat sac and the posterior layer of Gerota fascia can be separated to expose the lateral and dorsal side of adrenal tumor. At the third level, the adipose tissue at the bottom of adrenal gland and the surface tissue of renal parenchyma are separated, and the bottom of tumor is exposed by separation of tissue[4].

The right central adrenal vein starts from the apex of the adrenal gland and flows into the back of the inferior vena cava, and attention should be paid to the protection of the inferior vena cava when handling the right vein. The left central adrenal vein starts from the bottom of the left adrenal gland and flows into the left renal vein, and attention should be paid to the protection of the left renal vein[7]. The central adrenal vein and other blood vessels are isolated and ligated with hemo-lock.

DEFINITION AND CLINICAL TREATMENT OF COMPLEX ADRENAL TUMORS

Due to the deep location, complex adrenal tumors are closely related to large blood vessels, the tumor diameter is large, and the pathology is diverse. In recent years, some literature calls adrenal tumors with the following characteristics as complex adrenal tumors: (1) Large adrenal tumors (> 6.0 cm); (2) Adrenal pheochromocytoma; (3) Adrenal tumors with compression or invasion of peripheral blood vessels; (4) Obesity combined with suprarenal gland tumors (body mass index [BMI] ≥ 25 kg/m^2); (5) The tumors that need to preserve adrenal tissue during operation; (6) Adrenal malignant tumors; and (7) Having a history of retroperitoneal surgery[8,9].

The growth of the tumor is accompanied by the increase of the degree of malignancy, as well as the internal bleeding and necrosis of the tumor, resulting in the adhesion of the tumor and the surrounding organs, tissues, and blood vessels, which increases the difficulty of operation[10]. Gong *et al*[11] found that all operations were not converted to open surgery by using retroperitoneal laparoscopic technique to remove adrenal tumors larger than 8 cm. At the same time, they temporarily blocked the renal artery to reduce tumor bleeding. After 7-30 mo of follow-up, there was no tumor metastasis and recurrence, which proved that temporary blocking of the renal artery was a feasible and safe method in the treatment of huge adrenal tumors[11].

The pathology of pheochromocytoma can be divided into benign and malignant. Most of them are benign. Benign tumors are round or oval with a smooth surface. Pheochromocytoma can secrete catecholamines, causing hypertension, headache, sweating, palpitation, and other symptoms. Patients usually have persistent or paroxysmal hypertension before treatment. Therefore, perioperative management is an important part of laparoscopic resection of pheochromocytoma[12]. Recently, with the development of laparoscopic technology, the reports of retroperitoneal laparoscopic resection of benign and malignant pheochromocytoma gradually have increased. Costa *et al* performed retroperitoneal laparoscopic surgery on ten cases of adrenal tumors, including two cases of pheochromocytoma and one huge cystic pheochromocytoma (diameter: 14 cm). There were no complications during and after the operation, and the tumor did not recur during the follow-up[13].

Giant pheochromocytoma (> 6 cm) usually has a high degree of malignancy and easy to cause changes in the circulatory system of patients during the operation, resulting in blood pressure fluctuations. Similarly, the advantage of retroperitoneoscopy for giant pheochromocytoma is better than that of laparoscopy[14,15]. Shiraishi *et al*[14] found that in patients with huge pheochromocytoma, compared with laparoscopy, retroperitoneoscopy has obvious advantages in operation time and intraoperative bleeding. No recurrence or metastasis was found in postoperative follow-up. Laparoscopic surgery may be a safe and feasible method for pheochromocytoma treatment, preoperative preparation, intraoperative blood pressure, and postoperative active care.

Because of the hypertrophy of abdominal muscle and fat around the adrenal gland in obese patients, laparoscopic surgery was often contraindicated in the past. In recent years, studies have reported that single obesity is no longer a taboo for laparoscopic surgery[16,17]. When comparing the patients with a BMI > 40 kg/m^2, bilateral adrenal tumors, and abdominal surgery history who underwent laparoscopy and retroperitoneoscopy in the early stage, Arezzo *et al*[18] found that there was no significant difference in operation time, blood loss, or ambulation time between the two methods, and the eating time and recovery period after retroperitoneoscopy were significantly shortened. When comparing 41 obese patients with adrenal tumor (BMI ≥ 30 kg/m^2) and 96 non-obese patients (BMI < 30 kg/m^2) who underwent retroperitoneal laparoscopic surgery, it was found that the operation time for obese patients was significantly prolonged, and other parameters had no significant difference. The results showed that retroperitoneal laparoscopic surgery could be performed in obese patients with short recovery time and less bleeding[19]. Dickson *et al*[20] performed retroperitoneal laparoscopic adrenalectomy on 118 patients, 48% of whom had a BMI ≥

30 kg/m^2, and the patients recovered well without obvious intraoperative and postoperative complications. The above studies show that retroperitoneal laparoscopy is a safe and effective treatment for obese patients with adrenal tumors, which can be carried out in patients according to the clinical experience of surgeons.

Adrenal malignant tumors include adrenal cortical carcinoma, malignant pheochromocytoma, adrenal metastatic carcinoma, and adrenal lymphoma[21]. Most adrenocortical carcinomas are larger than 5 cm in diameter, with hemorrhage and necrosis. At the same time, with the tumor volume increasing, tumor cells are easy to invade the surrounding tissues, blood vessels, and nerves, increasing the difficulty of surgery. In the past, open surgery was recommended for adrenocortical carcinoma, with wide field of vision and complete exposure of tumor tissue, which was convenient for complete resection of the whole tumor tissue. With the development of laparoscopic technology, laparoscopic technology has been applied to adrenal cortical carcinoma. Ma *et al*[22] performed anatomical retroperitoneal laparoscopic surgery on 75 patients with adrenal metastasis. The pathological results showed that clear cell carcinoma and small cell lung cancer were the majority, and the local recurrence rate was 5.3%. Studies have found that BMI, tumor type, and positive margin are independent prognostic factors. Retroperitoneal laparoscopic technique is a safe and effective treatment for adrenal metastases[22].

Adrenal lesions are diverse, including adrenal adenoma, adrenal neuroblastoma, schwannoma, cyst, and other malignant lesions. Most adrenal lesions can be removed by laparoscopic technique[23]. Adrenal lymphangioma is another kind of benign adrenal tumor. Gao *et al*[24] found that no intraoperative or postoperative complications occurred in all patients through retroperitoneal laparoscopic technique for adrenal lymphangioma, and no tumor recurrence occurred during follow-up. Retroperitoneal ectopic pheochromocytoma is an-extra adrenal pheochromocytoma below the diaphragm and above the iliac fossa. It has abundant blood supply and is closely related to the peripheral blood vessels. Cai *et al*[25] performed retroperitoneal laparoscopic resection on four cases of retroperitoneal ectopic pheochromocytoma, of which one case was converted to laparotomy. All patients were operated successfully, without obvious intraoperative and postoperative complications, and the postoperative symptoms were significantly improved[25].

RECENT PROGRESS IN SURGICAL TREATMENT OF COMPLEX ADRENAL TUMORS

Recently, there are more and more reports on robot assisted laparoscopic technology. The disadvantages of traditional laparoscopic technology are the limited range of operation, the limited depth perception of 2D video image, and the unstable control of laparoscopic lens. The Da Vinci surgical robot system provides articulated instruments, 3D vision, tremor filtering, and stable cameras. It can make up for the defects of traditional laparoscopy. Surgeons can carry out operations under comfortable conditions[26,27]. In a recent meta-analysis, 1162 patients underwent adrenalectomy (747 patients received robotic adrenalectomy and 415 patients received conventional laparoscopic adrenalectomy). The study found that there were no significant differences in intraoperative and postoperative blood loss or mortality between the two groups. However, the hospital stay associated with robotic surgery was significantly shortened, and the operation time was significantly prolonged. The results showed that robotic surgery was a safe operation[28]. In another meta-analysis, 232 cases and 297 controls were included, including six prospective studies and two retrospective studies. The analysis showed that there was no difference in intraoperative and postoperative complications or mortality between the two groups, while the blood loss was significantly less and hospital stay was significantly shorter in the robot group[29]. Research shows that robotic laparoscopic surgery may be a safe and feasible surgical method for adrenal tumors, but further research is needed to prove it.

Robotic adrenalectomy can be divided into transperitoneal and retroperitoneal approaches. The preoperative preparation, patient position, and instrument channel placement of transperitoneal approach are similar to those of laparoscopic surgery. Transperitoneal approach has larger operation space and obvious anatomical landmarks. Lateral position can push the abdominal viscera to the opposite side, so as to better expose the surgical area. In the supine position, both adrenal glands can be easily found. In the published studies[30,31], most of the patients were in lateral position through the abdominal approach, and the patients were inclined 30-60 degrees. The procedure of transperitoneal approach is similar to that of open surgery.

Table 1 Important papers cited in this manuscript

No.	Ref.	Title	Journal
1	Gagner *et al*[1], 1992	Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma	*N Engl J Med*
2	Walz *et al*[1], 1996	Posterior retroperitoneoscopy as a new minimally invasive approach for adrenalectomy: Results of 30 adrenalectomies in 27 patients	*World J Surg*
3	Simone *et al*[5], 2019	Robot-assisted partial adrenalectomy for the treatment of Conn's syndrome: Surgical technique, and perioperative and functional outcomes	*Eur Urol*
4	Jiang *et al*[12], 2020	Comparison of the retroperitoneal versus transperitoneal laparoscopic adrenalectomy perioperative outcomes and safety for pheochromocytoma: A meta-analysis	*BMC Surg*
5	Shiraishi *et al* [14], 2019	Transperitoneal versus retroperitoneal laparoscopic adrenalectomy for large pheochromocytoma: Comparative outcomes	*Int J Urol Off J Japanese Urol Assoc*
6	Bai *et al*[15], 2019	Comparison of transperitoneal laparoscopic versus open adrenalectomy for large pheochromocytoma: A retrospective propensity score-matched cohort study	*Int J Surg*
7	Dickson *et al* [20], 2011	Posterior retroperitoneoscopic adrenalectomy: A contemporary American experience	*J Am Coll Surg*
8	Abraham *et al* [23], 2014	Laparoscopic extirpation of giant adrenal ganglioneuroma	*J Minim Access Surg*
9	Ji *et al*[26], 2020	Retrospective comparison of three minimally invasive approaches for adrenal tumors: perioperative outcomes of transperitoneal laparoscopic, retroperitoneal laparoscopic and robot-assisted laparoscopic adrenalectomy	*BMC Urol*
10	Conzo *et al* [28], 2016	Minimally invasive approach for adrenal lesions: Systematic review of laparoscopic versus retroperitoneoscopic adrenalectomy and assessment of risk factors for complications	*Int J Surg*

The operation does not enter the abdominal cavity, so many intra-abdominal complications are avoided, such as pleural injury, abdominal visceral organ injury, postoperative adhesion, and so on. Therefore, this approach is more suitable for patients with a history of abdominal surgery. But the disadvantage is that the operation space is limited, which increases the difficulty of operation. Kim *et al*[32] found that retroperitoneal robotic adrenalectomy has a shorter learning curve, and for huge adrenal tumors, retroperitoneal robotic adrenalectomy has shorter operation time and less postoperative pain than laparoscopic surgery.

Single port laparoscopic surgery (LESS) is a minimally invasive surgery that is being explored and optimized, that is, the lens and operating instruments are put into the abdominal cavity at the same time through an incision. The utility model has the advantages of small skin trauma, good aesthetic effect, less pain, and less incision complications. The disadvantage is that the cross use of single hole instruments increases the difficulty of the operation[33]. Including a total of 704 cases, a meta-analysis comparing laparoscopic single point adrenalectomy (LESSA) with conventional laparoscopic adrenalectomy. It was found that there were no significant differences in operation time, blood loss, eating time, analgesic dose, perioperative complications, or analgesic drugs between the two techniques, and LESS had a shorter hospital stay and lower postoperative pain score[34]. In another cohort study, 51 obese patients underwent LESS for retroperitoneal laparoscopic adrenalectomy, and the surgical results were compared with those of 65 obese patients who received standard retroperitoneal adrenalectomy by the same surgeon. The study found that there was no significant difference in hospital stay or surgical complications between the two groups, and there was also no significant difference in incision recovery time, postoperative pain requirements, or operation time. However, there were obvious advantages in satisfaction with incision appearance[35]. The results show that single port laparoscopic surgery is a feasible and safe method among experienced surgeons.

CONCLUSION

Laparoscopic adrenalectomy is the gold standard for the treatment of adrenal surgical diseases. At present, there is no unified standard for the surgical treatment of complex adrenal tumors. More and more studies have reported that retroperitoneal laparoscopic adrenalectomy for complex adrenal tumors has good postoperative recovery, exact surgical effect, and increasing application (Table 1). Robot assisted laparoscopy is

a minimally invasive technology developed in recent years. The combination of laparoscopy and robot not only has the advantages of minimally invasive laparoscopy, but also has the characteristics of flexible robot, which has a huge advantage in the treatment of adrenal tumors. However, there are few reports on the treatment of complex adrenal tumors by robot. Further research is needed to determine the role and efficacy of robot in complex adrenal tumor resection. With the progress of science and technology and the continuous improvement of surgeons' technical level, the surgical treatment of complex adrenal tumors will have more obvious advantages and curative effect in the future.

REFERENCES

1 **Gagner M**, Lacroix A, Bolté E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med* 1992; **327**: 1033 [PMID: 1387700 DOI: 10.1056/NEJM199210013271417]

2 **Walz MK**, Peitgen K, Hoermann R, Giebler RM, Mann K, Eigler FW. Posterior retroperitoneoscopy as a new minimally invasive approach for adrenalectomy: results of 30 adrenalectomies in 27 patients. *World J Surg* 1996; **20**: 769-774 [PMID: 8678949 DOI: 10.1007/s002689900117]

3 **Mercan S**, Seven R, Ozarmagan S, Tezelman S. Endoscopic retroperitoneal adrenalectomy. *Surgery* 1995; **118**: 1071-5; discussion 1075 [PMID: 7491525 DOI: 10.1016/s0039-6060(05)80116-3]

4 **Shi TP**, Zhang X, Ma X, Li HZ, Zhu J, Wang BJ, Gao JP, Cai W, Dong J. Laparoendoscopic single-site retroperitoneoscopic adrenalectomy: a matched-pair comparison with the gold standard. *Surg Endosc* 2011; **25**: 2117-2124 [PMID: 21170658 DOI: 10.1007/s00464-010-1506-z]

5 **Simone G**, Anceschi U, Tuderti G, Misuraca L, Celia A, De Concilio B, Costantini M, Stigliano A, Minisola F, Ferriero M, Guaglianone S, Gallucci M. Robot-assisted Partial Adrenalectomy for the Treatment of Conn's Syndrome: Surgical Technique, and Perioperative and Functional Outcomes. *Eur Urol* 2019; **75**: 811-816 [PMID: 30077398 DOI: 10.1016/j.eururo.2018.07.030]

6 **Li H**, Zhao T, Wei Q, Yuan H, Cao D, Shen P, Liu L, Zeng H, Chen N. Laparoscopic resection of a huge mature cystic teratoma of the right adrenal gland through retroperitoneal approach: a case report and literature review. *World J Surg Oncol* 2015; **13**: 318 [PMID: 26582506 DOI: 10.1186/s12957-015-0734-z]

7 **Wang B**, Ma X, Li H, Shi T, Hu D, Fu B, Lang B, Chen G, Zhang X. Anatomic retroperitoneoscopic adrenalectomy for selected adrenal tumors >5 cm: our technique and experience. *Urology* 2011; **78**: 348-352 [PMID: 21705044 DOI: 10.1016/j.urology.2011.02.035]

8 **Hupe MC**, Imkamp F, Merseburger AS. Minimally invasive approaches to adrenal tumors: an up-to-date summary including patient position and port placement of laparoscopic, retroperitoneoscopic, robot-assisted, and single-site adrenalectomy. *Curr Opin Urol* 2017; **27**: 56-61 [PMID: 27533502 DOI: 10.1097/MOU.0000000000000339]

9 **Raveendran V**, Koduveli RM, Adiyat KT. Robotic excision of complex adrenal mass with retrocaval extension and encasement of renal hilum with renal preservation. *Int Braz J Urol* 2018; **44**: 1261 [PMID: 29697927 DOI: 10.1590/S1677-5538.IBJU.2017.0384]

10 **De Crea C**, Raffaelli M, D'Amato G, Princi P, Gallucci P, Bellantone R, Lombardi CP. Retroperitoneoscopic adrenalectomy: tips and tricks. *Updates Surg* 2017; **69**: 267-270 [PMID: 28612211 DOI: 10.1007/s13304-017-0469-1]

11 **Gong B**, Ma M, Xie W, Yang X, Sun T. Retroperitoneal laparoscopic adrenalectomy with transient renal artery occlusion for large adrenal tumors (≥8 cm). *J Surg Oncol* 2018; **117**: 1066-1072 [PMID: 29448302 DOI: 10.1002/jso.25002]

12 **Jiang YL**, Qian LJ, Li Z, Wang KE, Zhou XL, Zhou J, Ye CH. Comparison of the retroperitoneal *vs* Transperitoneal laparoscopic Adrenalectomy perioperative outcomes and safety for Pheochromocytoma: a meta-analysis. *BMC Surg* 2020; **20**: 12 [PMID: 31931809 DOI: 10.1186/s12893-020-0676-4]

13 **Costa Almeida CE**, Caroço T, Silva MA, Albano MN, Louro JM, Carvalho LF, Costa Almeida CM. Posterior retroperitoneoscopic adrenalectomy-Case series. *Int J Surg Case Rep* 2018; **51**: 174-177 [PMID: 30173077 DOI: 10.1016/j.ijscr.2018.08.044]

14 **Shiraishi K**, Kitahara S, Ito H, Oba K, Ohmi C, Matsuyama H. Transperitoneal *vs* retroperitoneal laparoscopic adrenalectomy for large pheochromocytoma: Comparative outcomes. *Int J Urol* 2019; **26**: 212-216 [PMID: 30430653 DOI: 10.1111/iju.13838]

15 **Bai S**, Yao Z, Zhu X, Li Z, Jiang Y, Wang R, Wu B. Comparison of transperitoneal laparoscopic *vs* open adrenalectomy for large pheochromocytoma: A retrospective propensity score-matched cohort study. *Int J Surg* 2019; **61**: 26-32 [PMID: 30503601 DOI: 10.1016/j.ijsu.2018.11.018]

16 **Mohammadi-Fallah MR**, Mehdizadeh A, Badalzadeh A, Izadseresht B, Dadkhah N, Barbod A, Babaie M, Hamedanchi S. Comparison of transperitoneal *vs* retroperitoneal laparoscopic adrenalectomy in a prospective randomized study. *J Laparoendosc Adv Surg Tech A* 2013; **23**: 362-366 [PMID: 23573882 DOI: 10.1089/lap.2012.0301]

17 **Zonča P**, Bužga M, Ihnát P, Martínek L. Retroperitoneoscopic Adrenalectomy in Obese Patients: Is It Suitable? *Obes Surg* 2015; **25**: 1203-1208 [PMID: 25398550 DOI: 10.1007/s11695-014-1475-8]

18 **Arezzo A**, Bullano A, Cochetti G, Cirocchi R, Randolph J, Mearini E, Evangelista A, Ciccone G,

Bonjer HJ, Morino M. Transperitoneal *vs* retroperitoneal laparoscopic adrenalectomy for adrenal tumours in adults. *Cochrane Database Syst Rev* 2018; **12**: CD011668 [PMID: 30595004 DOI: 10.1002/14651858.CD011668.pub2]

19 **Kozłowski T**, Choromanska B, Wojskowicz P, Astapczyk K, Łukaszewicz J, Rutkowski D, Dadan J, Rydzewska-Rosołowska A, Myśliwiec P. Laparoscopic adrenalectomy: lateral transperitoneal *vs* posterior retroperitoneal approach - prospective randomized trial. *Wideochir Inne Tech Maloinwazyjne* 2019; **14**: 160-169 [PMID: 31118978 DOI: 10.5114/wiitm.2019.84694]

20 **Dickson PV**, Jimenez C, Chisholm GB, Kennamer DL, Ng C, Grubbs EG, Evans DB, Lee JE, Perrier ND. Posterior retroperitoneoscopic adrenalectomy: a contemporary American experience. *J Am Coll Surg* 2011; **212**: 659-65; discussion 665 [PMID: 21463807 DOI: 10.1016/j.jamcollsurg.2010.12.023]

21 **Baisakh MR**, Mohapatra N, Adhikary SD, Routray D. Malignant peripheral nerve sheath tumor of adrenal gland with heterologus osseous differentiation in a case of Von Recklinghausen's disease. *Indian J Pathol Microbiol* 2014; **57**: 130-132 [PMID: 24739852 DOI: 10.4103/0377-4929.130924]

22 **Ma X**, Li H, Zhang X, Huang Q, Wang B, Shi T, Hu D, Ai Q, Liu S, Gao J, Yang Y, Dong J, Zheng T. Modified anatomical retroperitoneoscopic adrenalectomy for adrenal metastatic tumor: technique and survival analysis. *Surg Endosc* 2013; **27**: 992-999 [PMID: 23239289 DOI: 10.1007/s00464-012-2553-4]

23 **Abraham GP**, Siddaiah AT, Das K, Krishnamohan R, George DP, Abraham JJ, Chandramathy SK. Laparoscopic extirpation of giant adrenal ganglioneuroma. *J Minim Access Surg* 2014; **10**: 45-47 [PMID: 24501511 DOI: 10.4103/0972-9941.124479]

24 **Gao L**, Zhang S, Wang H, Qiu Y, Yang L, Yuan J, Wei Q, Han P. Clinical and pathological characteristics of adrenal lymphangioma treated by laparoscopy *via* a retroperitoneal approach: experience and analysis of 7 cases. *Int J Clin Exp Med* 2015; **8**: 4212-4219 [PMID: 26064332]

25 **Cai H**, Zhang Y, Hu Z. Laparoscopic resection of ectopic pheochromocytoma. *Intractable Rare Dis Res* 2017; **6**: 203-205 [PMID: 28944143 DOI: 10.5582/irdr.2017.01051]

26 **Ji C**, Lu Q, Chen W, Zhang F, Ji H, Zhang S, Zhao X, Li X, Zhang G, Guo H. Retrospective comparison of three minimally invasive approaches for adrenal tumors: perioperative outcomes of transperitoneal laparoscopic, retroperitoneal laparoscopic and robot-assisted laparoscopic adrenalectomy. *BMC Urol* 2020; **20**: 66 [PMID: 32517679 DOI: 10.1186/s12894-020-00637-y]

27 **Ball MW**, Hemal AK, Allaf ME. International Consultation on Urological Diseases and European Association of Urology International Consultation on Minimally Invasive Surgery in Urology: laparoscopic and robotic adrenalectomy. *BJU Int* 2017; **119**: 13-21 [PMID: 27431446 DOI: 10.1111/bju.13592]

28 **Conzo G**, Tartaglia E, Gambardella C, Esposito D, Sciascia V, Mauriello C, Nunziata A, Siciliano G, Izzo G, Cavallo F, Thomas G, Musella M, Santini L. Minimally invasive approach for adrenal lesions: Systematic review of laparoscopic *vs* retroperitoneoscopic adrenalectomy and assessment of risk factors for complications. *Int J Surg* 2016; **28** Suppl 1: S118-S123 [PMID: 26708860 DOI: 10.1016/j.ijsu.2015.12.042]

29 **Tang K**, Li H, Xia D, Yu G, Guo X, Guan W, Xu H, Ye Z. Robot-assisted *vs* laparoscopic adrenalectomy: a systematic review and meta-analysis. *J Laparoendosc Adv Surg Tech A* 2015; **25**: 187-195 [PMID: 25763475 DOI: 10.1089/lap.2014.0431]

30 **Agrusa A**, Romano G, Navarra G, Conzo G, Pantuso G, Buono GD, Citarrella R, Galia M, Monte AL, Cucinella G, Gulotta G. Innovation in endocrine surgery: robotic *vs* laparoscopic adrenalectomy. Meta-analysis and systematic literature review. *Oncotarget* 2017; **8**: 102392-102400 [PMID: 29254254 DOI: 10.18632/oncotarget.22059]

31 **Okoh AK**, Berber E. Laparoscopic and robotic adrenal surgery: transperitoneal approach. *Gland Surg* 2015; **4**: 435-441 [PMID: 26425457 DOI: 10.3978/j.issn.2227-684X.2015.05.03]

32 **Kim WW**, Lee YM, Chung KW, Hong SJ, Sung TY. Comparison of Robotic Posterior Retroperitoneal Adrenalectomy over Laparoscopic Posterior Retroperitoneal Adrenalectomy: A Single Tertiary Center Experience. *Int J Endocrinol* 2019; **2019**: 9012910 [PMID: 31885564 DOI: 10.1155/2019/9012910]

33 **Brandao LF**, Autorino R, Laydner H, Haber GP, Ouzaid I, De Sio M, Perdonà S, Stein RJ, Porpiglia F, Kaouk JH. Robotic *vs* laparoscopic adrenalectomy: a systematic review and meta-analysis. *Eur Urol* 2014; **65**: 1154-1161 [PMID: 24079955 DOI: 10.1016/j.eururo.2013.09.021]

34 **Wu S**, Lai H, Zhao J, Chen J, Mo X, Zuo H, Lin Y. Laparoendoscopic Single-site Adrenalectomy *vs* Conventional Laparoscopic Adrenalectomy: An Updated Meta Analysis. *Urol J* 2016; **13**: 2590-2598 [PMID: 27085558 DOI: 10.22037/uj.v13i2.3218]

35 **Wang Y**, He Y, Li BS, Wang CH, Chen Z, Lu ML, Wen ZQ, Chen X. Laparoendoscopic Single-Site Retroperitoneoscopic Adrenalectomy Versus Conventional Retroperitoneoscopic Adrenalectomy in Obese Patients. *J Endourol* 2016; **30**: 306-311 [PMID: 26486758 DOI: 10.1089/end.2015.0526]

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LETTER TO THE EDITOR

How is artificial intelligence applied in solid tumor imaging?

Jian-She Yang, Qiang Wang

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Abstract

How is artificial intelligence (AI) applied in solid tumor imaging? What is the essential value of AI for tumor precision diagnosis and can it wholly replace the human beings? Some opinions in this letter should be considered.

Key Words: Artificial intelligence; Tumor; Imaging; Diagnosis

Core Tip: Artificial intelligence has been widely applied in tumor diagnosis due to its precise recognition and big-data handling properties, which can relieve the clinicians from the diagnostic workloads. However, this model, to some extent, is rigid, and cannot completely replace the human beings eventually. How to promote and optimize it with real intelligence has a long way to go.

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TO THE EDITOR

We have read the review article by Shao *et al*[1], who described that artificial intelligence (AI) has greatly relieved clinical workloads and changed the current medical workflows, and summarized its application outlines and priorities compared with traditional tumor diagnostic methods through reviewing related advances in this area. This aim is proper, but the authors have not done it well.

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This topic is of great interest, and needs to be further investigated for a long period of time in the future. However, the authors have not outlined and described it in a rational way. The obvious shortcomings of this review are described as follows:

Given that the authors aimed to discuss the application of AI in solid tumor imaging, they should have depicted all types of solid tumors as systematically as possible, in that the solid tumors present diverse characteristics in terms of their physical and chemical nature, which are the bases that AI works on. However, the authors have failed to provide readers with enough systematical information, and with a holistic vision of AI working on solid tumors.

A review article should not only describe the phenomena alone, but it should also discuss the potential mechanism. The common mechanisms of AI seem to be well-known, but there is a lack of description for interactive episode in this review.

Concise and precise graphs will inevitably improve the quality of the article, but the authors have not made use of these.

AI, sometimes, can resolve the difficulties that other advanced technologies or human beings could not do. Thus, in this review, the authors should have made great efforts to describe how AI processes images. Whether AI can recognize the diversity of the graphic grayscale, special molecules, or even some metal ions, and how it works? How does AI distinguish the tumor from the surrounding tissues? All of these principles and advancements should be clarified as detailed as possible.

Additionally, although the authors wanted to describe and summarize the advances and advantages of AI, they failed to provide more information systematically, but only listed amounts of dispersive works, without any graphs highlighting the AI characteristics.

REFERENCES

1 **Shao Y**, Zhang YX, Chen HH, Lu SS, Zhang SC, Zhang JX. Advances in the application of artificial intelligence in solid tumor imaging. *Artif Intell Cancer* 2021; **2**: 12-24 [DOI: 10.35713/aic.v2.i2.12]

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OPINION REVIEW

Artificial neural network for prediction of acute kidney injury after liver transplantation for cirrhosis and hepatocellular carcinoma

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Abstract

Acute kidney injury (AKI) has serious consequences on the prognosis of patients undergoing liver transplantation (LT) for liver cancer and cirrhosis. Artificial neural network (ANN) has recently been proposed as a useful tool in many fields in the setting of solid organ transplantation and surgical oncology, where patient prognosis depends on a multidimensional and nonlinear relationship between variables pertaining to the surgical procedure, the donor (graft characteristics), and the recipient comorbidities. In the specific case of LT, ANN models have been developed mainly to predict survival in patients with cirrhosis, to assess the best donor-to-recipient match during allocation processes, and to foresee postoperative complications and outcomes. This is a specific opinion review on the role of ANN in the prediction of AKI after LT for liver cancer and cirrhosis, highlighting potential strengths of the method to forecast this serious postoperative complication.

Key Words: Liver transplantation; Acute kidney injury; Artificial neural network; Prediction; Hepatocellular carcinoma; Postoperative

Core Tip: This opinion review aims to explore the potential benefits of artificial neural network models in predicting the occurrence of acute kidney injury in the postoperative period of liver transplantation for cirrhosis and hepatocellular carcinoma.

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INTRODUCTION

Liver transplantation (LT) is the best treatment option for patients with early stages of hepatocellular carcinoma (HCC) and cirrhosis[1-4]. Mainly, the use of LT depends on maintaining a balance between patient-specific survival benefit, the availability of alternative treatment modalities[5,6], and the equitable distribution of donor organs[5,7-12]. Current selection criteria aim to avoid transplant futility by excluding patients at a high risk of tumor recurrence[10,11]. Selecting patients with HCC within Milan criteria has been shown to provide excellent patient outcomes[13-15].

Among the possible complications related to LT for cirrhosis and HCC, acute kidney injury (AKI) is a common complication, with extremely variable reported incidence rates (4% to 94%)[16-22], and is associated with several immediate complications, including volume overload, metabolic acidosis and electrolyte disturbances. Although most patients eventually recover after an episode of AKI, many patients may not return to baseline renal function, and the occurrence of AKI has been shown to be an independent risk factor for the development of chronic kidney disease and death, as well as for the reduction of survival rates of liver receptors[23]. In addition, transplant patients who require temporary renal replacement therapy (RRT) have a prolonged hospital stay, with subsequent need for more resources and higher costs related to LT[24].

Artificial neural network (ANN) is commonly used to solve complex problems, where the behavior of variables is not rigorously known. One of its main characteristics is the ability to learn through examples and generalize the information learned, generating a non-linear model, making its application in spatial analysis very efficient [25]. ANN can be an alternative with high performance to the logistic regression (LR) model, where the relative risk term is parameterized by an ANN instead of regression, enabling the application of deep learning. ANN models have been developed mainly to predict survival in patients with cirrhosis, to assess the best donor-to-recipient match during allocation processes, and to foresee postoperative complications and outcomes[26-32], but studies evaluating such a promising tool, as ANN, for predicting AKI following LT for cirrhosis and HCC, are scarce.

The multifactorial origin of AKI after LT makes it complex to predict which candidate for the procedure has an increased risk of this complication[33,34]. In the face of this complexity, ANN would be a very reliable prognostic tool for AKI risk assessment, enabling, therefore, early or even prophylactic therapies for AKI, improving patients outcomes[35]. This is a specific opinion review on the role of ANN in the prediction of AKI after LT for liver cancer and cirrhosis, highlighting potential strengths of the method to forecast this serious postoperative complication.

OVERVIEW OF RISK FACTORS FOR AKI AFTER LT

The etiology of AKI after LT is multifactorial and not fully understood, with several risk factors related to the organ receptor[20,22,24,35], graft-related characteristics[36], and finally some perioperative have been identified over the past few years[20,33,34]. Similarly, the use of postoperative nephrotoxic immunosuppression can further provoke or aggravate kidney damage[20].

Based on these risk factors, various models have been developed using LR for predicting AKI after LT. However, because several of these models address postoperative parameters, their utility in predictive modeling appears to be of questionable relevance. Regardless of the variability of the triggering factors, it is of fundamental importance to identify patients at risk ideally by the set of preoperative clinical assessment and complementary information of the intraoperative period, thus enabling the adoption of preventive measures or early therapies for AKI, such as reduced doses and postponing postoperative patients immunosuppression, and also early RRT, thus reducing mortality and accelerated recovery of renal function[20].

Among the potential AKI predictors that can be evaluated at the time of transplant indication, the severity of the recipient's liver disease stands out[20-37], expressed by the Model for End-Stage Liver Disease (MELD) score. The MELD score determines the allocation of the organ prioritizing the "sickest first" patient, with high values of the score conferring a greater risk for the occurrence of ARF after TH, thus reflecting an interrelationship between liver and renal functions in cirrhotic patients[38]. Similarly, another predictors related to the recipient have been identified, such as high levels of pre-transplant serum creatinine, high body mass index (BMI) of the recipient (BMI values above 30 kg/m^2), and the presence of pre-existing diabetes mellitus[33,35,37].

In addition to the clinical characteristics of the recipient, there are predictive factors of AKI that are related to the functional quality of the graft. The first situation refers to the modality of TH performed, as living-donor LT, in general, offers a graft that is functionally superior to deceased-donor LT, where the critical clinical conditions of the donor confer a greater potential risk to the occurrence of postoperative AKI[20]. Moreover, "marginal grafts" from "extended criteria donors" have increasingly been used, including steatotic grafts, grafts from clinically critical donors, grafts with high ischemia time, both "warm ischemia time" and "cold ischemia time"[20,37,39].

There are some intraoperative events that can be crucial for the occurrence of AKI. The main factor concerns the occurrence of intraoperative arterial hypotension (IOAH) with consequent renal hypoperfusion during LT[22]. Patients undergoing LT often experience IOAH as a result of several factors, including the duration of surgery, the severity of bleeding, the severity of post-reperfusion syndrome of the graft, and the severity of liver disease[33,35,39]. On some occasions, this renal hypoperfusion occurs in patients with previous renal dysfunction[34], and can often be aggravated by the deleterious renal effects of blood transfusion[22,34,37] and the use of vasoactive drugs in the intraoperative period[40].

BASICS OF ANN

An ANN lies under the umbrella of reinforcement machine learning, and comprises 'units' arranged in a series of layers, each of which connects to layers on either side. ANNs are inspired by biological systems, such as the brain, and how they process information. The original concept of ANNs is derived from neurobiological models. ANNs are massively parallel, computer-intensive and data-driven algorithmic system that is composed of multitude of highly interconnected nodes (neurons). Each elementary node of a neural network is able to receive an input from external sources, according to the relative importance and different weight, which transforms into an output signal to other nodes by different activation function[25].

In terms of topology, to implement an ANN, different variables must be defined, among which: (1) the number of nodes in the input layer (such variable corresponds to the number of variables that will be used to feed the neural network, being normally the variables of greater importance for the problem under study); (2) the number of hidden layers and the number of neurons to be placed in these layers; and (3) the number of neurons in the output layer[41].

The process of learning of an ANN is a process where free parameters are adapted through a process of stimulation by the environment in which the network is inserted. With this, the type of learning is determined based on the way in which the modification of the parameters takes place. In summary, there is the following sequence of events: (1) the neural network is stimulated by an environment; (2) the neural network undergoes modifications in its free parameters as a result of this stimulation; and (3) the neural network responds in a new way to the environment, due to changes in its internal structure[25].

Considering the interactions of linked nodes, an output obtained from one node can serve as an input for other nodes, and the conversion of inputs into outputs is activated by virtue of certain transforming function that is typically monotone. The specified working function depends on parameters determined for the training set of inputs and outputs. The network architecture is the organization of nodes and the types of connections permitted. The nodes are arranged in a series of layers with connections between nodes in different layers, but not between nodes in the same layer[42].

ANNs can be classified into feedforward and feedback networks categories, and back-propagation updating algorithm with adjustment of connection weights between the neurons during the training process, is a widely used feedforward networks. Feedforward networks is included within the supervised learning network, essentially

using a gradient descent-training algorithm[43,44].

Multilayer perceptron

The perceptron, introduced by Rosenblatt in 1958, is a simple form of RNA whose main application is in pattern classification problems. The single-layer perceptron is only capable of classifying linearly separable patterns. In practice, the problem to be worked on does not admit an exact linear separation, making it necessary to use a multilayer perceptron. Multilayer perceptron (MLP)-type architectures are the most used and known artificial neural models. An MLP network is subdivided into layers: input layer, intermediate or hidden layer(s) and output layer. In the multilayer ANN architecture, inputs are extended from the input layer to the output layer, passing through one or more hidden layers. In this same sense, a multilayer neural network is typically composed of aligned layers of neurons. The input layer distributes the input information to the hidden layer(s) of the network. At the output layer, the solution to the problem is obtained. Hidden layers are intermediate layers, whose function is to separate the input and output layers. Neurons in one layer are connected only to neurons in the immediately posterior layer, with no feedback or connections between neurons in the same layer. Also, characteristically, the layers are fully connected[45].

In Figure 1 it is possible to observe an MLP-type architecture with two intermediate layers. The presented network has all connections, which means that a neuron in any layer of the network is connected to all other neurons in the previous layer. Signals flow through the network positively, from left to right, layer by layer.

The learning process of MLP networks by back-propagation consists of two steps: propagation and back-propagation. In the propagation step, an activation pattern is applied to the nodes of the network's input layer and its effect propagates through the network, layer by layer. In the last layer, a set of outputs is produced, configured as the real network response. In the and back-propagation step, all synaptic weights are adjusted according to an error correction rule. The error signal is propagated backwards through the network, against the direction of the synaptic connections, the synaptic weights being adjusted to make the actual response of the network approach the desired response, in a statistical sense[25]. An important characteristic of MLP networks is the non-linearity of neuron outputs. This nonlinearity is obtained using a sigmoid-type function as an activation function, usually the logistic function[25].

ANNS FOR AKI PREDICTON AFTER LT FOR CIRRHOSIS AND HCC

Over the past two decades, machine learning algorithms have been increasingly applied for cancer diagnosis, prognostication, and treatment outcome prediction[46-49]. For example, recently, an MLA approach based on a random forest workflow has been developed by a group in Germany to predict disease-free survival after liver resection for HCC[50].

Studies regarding ANNs in the field of LT for cirrhosis and HCC, researchers[26-31] have already conducted studies with LR models and ANN for the prediction of survival of these patients (Table 1). In 1992, Doyle *et al*[26] introduced a 10 feed forward back-propagation ANN model to predict LT survival. Marsh *et al*[27] presented a three layer feed forward fully connected ANN model to predict the survival analysis and time to recurrence of HCC after LT. Parmanto *et al*[28] conducted a study with time series sequence of medical data of patients that undergone LT with ANNs using back-propagation through time algorithm, and their results were compared with 6-fold cross validation. Cucchetti *et al*[29] proposed an ANN survival prognosis model for patients with cirrhosis at a LT unit, and proved that ANN is better than MELD for this proposal. Zhang *et al*[30] proposed a MLP model of patients with cirrhosis and compared the performance of the model with MELD and Sequential Organ Failure Assessment score. In 2013, Cruz *et al*[31] conducted a study with radial basis function ANNs using multi-objective evolutionary algorithm in order to match the donor-recipient pairs.

The results of the researchers above demonstrate that the ANNs predictive models can be capable of using live data of cirrhotic patients with or without HCC, and perform both diagnostic and predictive tasks[32]. Because of the simplicity in structure, ability to do parallel processing tasks, having long term memory, having fault tolerant ability and getting collective output, ANN models can do better than LR models[51].

In the specific scenario of AKI after LT for cirrhosis and HCC, in 2018, Lee *et al*[52] compared the performance of machine learning approaches with that of LR analysis to

Table 1 Studies with artificial neural networks and logistic regression models for the prediction of survival of patients in the field of cirrhosis and liver transplantation

Ref.	Year	Model and endpoint
Doyle *et al* [26]	1992	10 feed forward back-propagation ANN model to predict LT survival
Marsh *et al* [27]	1997	ANN for survival analysis and time to recurrence of HCC after LT
Parmanto *et al*[28]	2001	Back-propagation through time ANN algorithm to predict outcomes after LT
Cucchetti *et al* [29]	2007	ANN for survival prognosis of patients with cirrhosis
Zhang *et al* [30]	2012	MLP model for predicting outcomes of patients with cirrhosis and compared the performance with MELD and SOFA scores
Cruz *et al*[31]	2013	Radial basis function ANNs using multi-objective evolutionary algorithm to match the donor-recipient pairs
Lee *et al*[52]	2018	Compared the performance of ML approaches (decision tree, random forest, gradient boosting machine, support vector machine, naïve Bayes, MLP, and deep belief networks) with that of LR analysis to predict AKI after LT for cirrhosis and HCC (49%)
He *et al*[53]	2021	LR analysis as a conventional model, and random forest, support vector machine, classical decision tree, and conditional inference tree algorithms to predict AKI after LT for cirrhosis and HCC (40.7%)

ANN: Artificial neural network; LR: Logistic regression; LT: Liver transplantation; HCC: Hepatocellular carcinoma; MLP: Multilayer perceptron; MELD: Model for end-stage liver disease; SOFA: Sequential Organ Failure Assessment; AKI: Acute kidney injury.

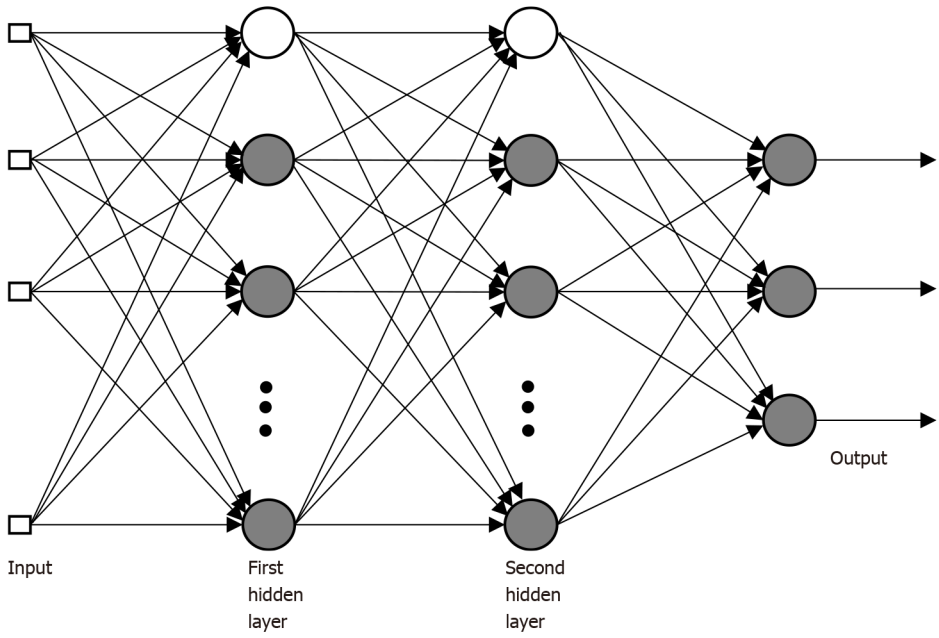

Figure 1 Multilayer perceptron-type architecture with two intermediate layers.

predict AKI after LT for cirrhosis and up to 49% of total patients with HCC. This huge analysis of 1211 patients adopted preoperative and intraoperative input variables. The primary outcome was postoperative AKI defined by Acute Kidney Injury Network criteria. The following machine learning techniques were used: decision tree, random forest, gradient boosting machine, support vector machine, naïve Bayes, MLP, and deep belief networks. These techniques were compared with LR analysis regarding the area under the receiver operating characteristic (AUROC). AKI incidence was 30.1%. The performance in terms of AUROC was best in gradient boosting machine among all analyses to predict AKI of all stages (0.90, 95%CI: 0.86–0.93), and decision tree and random forest techniques showed moderate performance (AUROC 0.86 and 0.85, respectively). The AUROC of the MLP was 0.64 (0.59–0.69), vector machine was 0.62 (0.57–0.67), naïve Bayes was 0.60 (0.54–0.65), and deep belief network was 0.59 (0.53–0.64). The AUROC of LR analysis was 0.61 (95%CI: 0.56–0.66), concluding that

MLP model showed best performance than LR analysis, with a slight higher, but significant, AUROC.

He *et al*[53] evaluated a total of 493 patients (40.7% of patients with HCC) with donation after cardiac death LT. In this study, AKI was defined according to the clinical practice guidelines of Kidney Disease Improving Global Outcomes, and the clinical data of patients with AKI and without AKI were compared through LR analysis as a conventional model, and four predictive machine learning models were developed using random forest, support vector machine, classical decision tree, and conditional inference tree algorithms. The predictive power of these models was then evaluated using the AUROC. The reported incidence of AKI was 35.7% (176/493) during the follow-up period. Compared with the non-AKI group, the AKI group showed a remarkably lower survival rate ($P < 0.001$). The random forest model demonstrated the highest prediction accuracy of 0.79 with AUROC of 0.850 (95%CI: 0.794–0.905), which was significantly higher than the AUCs of the other machine learning algorithms and LR models ($P < 0.001$).

As the standard ANN workflow involves model performance monitoring and re-training to account for model drift, a multidisciplinary partnership between clinicians and data scientists is required, with a commitment to the curation and iterative maintenance of datasets to allow for the development of meaningful decision-support tools[54]. This process should involve, first and foremost, a robust, consistent, and objective means of collecting data. The data in the case of postoperative AKI, are mainly laboratorial and clinicopathologic characteristics from electronic medical records, and clinicians and surgeons must to establish interdisciplinary partnerships that strive towards a common goal and synergism. For instance, clinicians and surgeons help provide a clinically relevant outcome, and data scientists can identify the optimal methodology to make predictions for the outcome based on the available data.

CONCLUSION

The reported high incidence of AKI after LT for cirrhosis and HCC in numerous studies highlights the importance of this issue. The prediction of this complication may provide a focus for further research, mainly in the development of ANNs predictive models that may be applied immediately after LT.

ANNs are essentially a large number of interconnected processing elements, working in unison to solve specific problems, and its use for this specific purpose is directly related to the efficiency with which it provides responses close to real output data. ANN methods may provide feasible tools for forecasting AKI after LT in this population, and perhaps provide a high-performance predictive model that may ultimately improve perioperative management of these patients at risk for this serious complication.

REFERENCES

1 **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

2 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]

3 **Bruix J**, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016; **150**: 835-853 [PMID: 26795574 DOI: 10.1053/j.gastro.2015.12.041]

4 **European Association For The Study Of The Liver**; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

5 **Johnson RJ**, Bradbury LL, Martin K, Neuberger J; UK Transplant Registry. Organ donation and transplantation in the UK-the last decade: a report from the UK national transplant registry. *Transplantation* 2014; **97** Suppl 1: S1-S27 [PMID: 24356460 DOI: 10.1097/01.TP.0000438215.16737.68]

6 **Neuberger J**, James O. Guidelines for selection of patients for liver transplantation in the era of donor-organ shortage. *Lancet* 1999; **354**: 1636-1639 [PMID: 10560692 DOI: 10.1016/S0140-6736(99)90002-8]

7 **Kwong A**, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Foutz J, Miller E, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Liver. *Am J Transplant*

2020; **20** Suppl s1: 193-299 [PMID: 31898413 DOI: 10.1111/ajt.15674]
8 **Freeman RB**, Edwards EB, Harper AM. Waiting list removal rates among patients with chronic and malignant liver diseases. *Am J Transplant* 2006; **6**: 1416-1421 [PMID: 16686765 DOI: 10.1111/j.1600-6143.2006.01321.x]
9 **Northup PG**, Intagliata NM, Shah NL, Pelletier SJ, Berg CL, Argo CK. Excess mortality on the liver transplant waiting list: unintended policy consequences and Model for End-Stage Liver Disease (MELD) inflation. *Hepatology* 2015; **61**: 285-291 [PMID: 24995689 DOI: 10.1002/hep.27283]
10 **Mehta N**, Dodge JL, Goel A, Roberts JP, Hirose R, Yao FY. Identification of liver transplant candidates with hepatocellular carcinoma and a very low dropout risk: implications for the current organ allocation policy. *Liver Transpl* 2013; **19**: 1343-1353 [PMID: 24285611 DOI: 10.1002/lt.23753]
11 **Mazzaferro V**, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, Camerini T, Milione M, Regalia E, Spreafico C, Gangeri L, Buzzoni R, de Braud FG, De Feo T, Mariani L. The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors. *Am J Transplant* 2016; **16**: 2892-2902 [PMID: 27134017 DOI: 10.1111/ajt.13831]
12 **Yeh H**, Smoot E, Schoenfeld DA, Markmann JF. Geographic inequity in access to livers for transplantation. *Transplantation* 2011; **91**: 479-486 [PMID: 21200366 DOI: 10.1097/TP.0b013e3182066275]
13 **Mazzaferro V**. Squaring the circle of selection and allocation in liver transplantation for HCC: An adaptive approach. *Hepatology* 2016; **63**: 1707-1717 [PMID: 26703761 DOI: 10.1002/hep.28420]
14 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]
15 **Mazzaferro V**, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, Cescon M, Di Sandro S, Yi-Feng H, Lauterio A, Bongini M, Cucchetti A. Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma. *Gastroenterology* 2018; **154**: 128-139 [PMID: 28989060 DOI: 10.1053/j.gastro.2017.09.025]
16 **Hamada M**, Matsukawa S, Shimizu S, Kai S, Mizota T. Acute kidney injury after pediatric liver transplantation: incidence, risk factors, and association with outcome. *J Anesth* 2017; **31**: 758-763 [PMID: 28766021 DOI: 10.1007/s00540-017-2395-2]
17 **Chae MS**, Lee N, Park DH, Lee J, Jung HS, Park CS, Choi JH, Hong SH. Influence of oxygen content immediately after graft reperfusion on occurrence of postoperative acute kidney injury in living donor liver transplantation. *Medicine (Baltimore)* 2017; **96**: e7626 [PMID: 28767577 DOI: 10.1097/MD.0000000000007626]
18 **Mizota T**, Hamada M, Matsukawa S, Seo H, Tanaka T, Segawa H. Relationship Between Intraoperative Hypotension and Acute Kidney Injury After Living Donor Liver Transplantation: A Retrospective Analysis. *J Cardiothorac Vasc Anesth* 2017; **31**: 582-589 [PMID: 28216198 DOI: 10.1053/j.jvca.2016.12.002]
19 **Kim WH**, Lee HC, Lim L, Ryu HG, Jung CW. Intraoperative Oliguria with Decreased SvO_2 Predicts Acute Kidney Injury after Living Donor Liver Transplantation. *J Clin Med* 2018; **8** [PMID: 30597881 DOI: 10.3390/jcm8010029]
20 **Kalisvaart M**, Schlegel A, Umbro I, de Haan JE, Polak WG, IJzermans JN, Mirza DF, Perera MTP, Isaac JR, Ferguson J, Mitterhofer AP, de Jonge J, Muiesan P. The AKI Prediction Score: a new prediction model for acute kidney injury after liver transplantation. *HPB (Oxford)* 2019; **21**: 1707-1717 [PMID: 31153834 DOI: 10.1016/j.hpb.2019.04.008]
21 **Zhou J**, Zhang X, Lyu L, Ma X, Miao G, Chu H. Modifiable risk factors of acute kidney injury after liver transplantation: a systematic review and meta-analysis. *BMC Nephrol* 2021; **22**: 149 [PMID: 33888081 DOI: 10.1186/s12882-021-02360-8]
22 **Joosten A**, Lucidi V, Ickx B, Van Obbergh L, Germanova D, Berna A, Alexander B, Desebbe O, Carrier FM, Cherqui D, Adam R, Duranteau J, Saugel B, Vincent JL, Rinehart J, Van der Linden P. Intraoperative hypotension during liver transplant surgery is associated with postoperative acute kidney injury: a historical cohort study. *BMC Anesthesiol* 2021; **21**: 12 [PMID: 33430770 DOI: 10.1186/s12871-020-01228-y]
23 **Chawla LS**, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, Bittleman D, Cruz D, Endre Z, Fitzgerald RL, Forni L, Kane-Gill SL, Hoste E, Koyner J, Liu KD, Macedo E, Mehta R, Murray P, Nadim M, Ostermann M, Palevsky PM, Pannu N, Rosner M, Wald R, Zarbock A, Ronco C, Kellum JA; Acute Disease Quality Initiative Workgroup 16. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017; **13**: 241-257 [PMID: 28239173 DOI: 10.1038/nrneph.2017.2]
24 **Hobson C**, Ozrazgat-Baslanti T, Kuxhausen A, Thottakkara P, Efron PA, Moore FA, Moldawer LL, Segal MS, Bihorac A. Cost and Mortality Associated With Postoperative Acute Kidney Injury. *Ann Surg* 2015; **261**: 1207-1214 [PMID: 24887982 DOI: 10.1097/SLA.0000000000000732]
25 **Haykin S**. Neural networks: Principles and Practice. New York: Bookman, 2001
26 **Doyle HR**, Dvorchik I, Mitchell S, Marino IR, Ebert FH, McMichael J, Fung JJ. Predicting outcomes after liver transplantation. A connectionist approach. *Ann Surg* 1994; **219**: 408-415 [PMID: 8161267

DOI: 10.1097/00000658-199404000-00012]
27 **Marsh JW**, Dvorchik I, Subotin M, Balan V, Rakela J, Popechitelev EP, Subbotin V, Casavilla A, Carr BI, Fung JJ, Iwatsuki S. The prediction of risk of recurrence and time to recurrence of hepatocellular carcinoma after orthotopic liver transplantation: a pilot study. *Hepatology* 1997; **26**: 444-450 [PMID: 9252157 DOI: 10.1002/hep.510260227]
28 **Parmanto B**, Doyle HR. Recurrent neural networks for predicting outcomes after liver transplantation: representing temporal sequence of clinical observations. *Methods Inf Med* 2001; **40**: 386-391 [PMID: 11776736]
29 **Cucchetti A**, Vivarelli M, Heaton ND, Phillips S, Piscaglia F, Bolondi L, La Barba G, Foxton MR, Rela M, O'Grady J, Pinna AD. Artificial neural network is superior to MELD in predicting mortality of patients with end-stage liver disease. *Gut* 2007; **56**: 253-258 [PMID: 16809421 DOI: 10.1136/gut.2005.084434]
30 **Zhang M**, Yin F, Chen B, Li YP, Yan LN, Wen TF, Li B. Pretransplant prediction of posttransplant survival for liver recipients with benign end-stage liver diseases: a nonlinear model. *PLoS One* 2012; **7**: e31256 [PMID: 22396731 DOI: 10.1371/journal.pone.0031256]
31 **Cruz-Ramírez M**, Hervás-Martínez C, Fernández JC, Briceño J, de la Mata M. Predicting patient survival after liver transplantation using evolutionary multi-objective artificial neural networks. *Artif Intell Med* 2013; **58**: 37-49 [PMID: 23489761 DOI: 10.1016/j.artmed.2013.02.004]
32 **Dreiseitl S**, Ohno-Machado L. Logistic regression and artificial neural network classification models: a methodology review. *J Biomed Inform* 2002; **35**: 352-359 [PMID: 12968784 DOI: 10.1016/s1532-0464(03)00034-0]
33 **Park MH**, Shim HS, Kim WH, Kim HJ, Kim DJ, Lee SH, Kim CS, Gwak MS, Kim GS. Clinical Risk Scoring Models for Prediction of Acute Kidney Injury after Living Donor Liver Transplantation: A Retrospective Observational Study. *PLoS One* 2015; **10**: e0136230 [PMID: 26302370 DOI: 10.1371/journal.pone.0136230]
34 **Zongyi Y**, Baifeng L, Funian Z, Hao L, Xin W. Risk factors of acute kidney injury after orthotopic liver transplantation in China. *Sci Rep* 2017; **7**: 41555 [PMID: 28134286 DOI: 10.1038/srep41555]
35 **Utsumi M**, Umeda Y, Sadamori H, Nagasaka T, Takaki A, Matsuda H, Shinoura S, Yoshida R, Nobuoka D, Satoh D, Fuji T, Yagi T, Fujiwara T. Risk factors for acute renal injury in living donor liver transplantation: evaluation of the RIFLE criteria. *Transpl Int* 2013; **26**: 842-852 [PMID: 23855657 DOI: 10.1111/tri.12138]
36 **Jochmans I**, Meurisse N, Neyrinck A, Verhaegen M, Monbaliu D, Pirenne J. Hepatic ischemia/reperfusion injury associates with acute kidney injury in liver transplantation: Prospective cohort study. *Liver Transpl* 2017; **23**: 634-644 [PMID: 28124458 DOI: 10.1002/lt.24728]
37 **Thongprayoon C**, Kaewput W, Thamcharoen N, Bathini T, Watthanasuntorn K, Lertjitbanjong P, Sharma K, Salim SA, Ungprasert P, Wijarnpreecha K, Kröner PT, Aeddula NR, Mao MA, Cheungpasitporn W. Incidence and Impact of Acute Kidney Injury after Liver Transplantation: A Meta-Analysis. *J Clin Med* 2019; **8** [PMID: 30884912 DOI: 10.3390/jcm8030372]
38 **Tinti F**, Umbro I, Meçule A, Rossi M, Merli M, Nofroni I, Corradini SG, Poli L, Pugliese F, Ruberto F, Berloco PB, Mitterhofer AP. RIFLE criteria and hepatic function in the assessment of acute renal failure in liver transplantation. *Transplant Proc* 2010; **42**: 1233-1236 [PMID: 20534269 DOI: 10.1016/j.transproceed.2010.03.128]
39 **Romano TG**, Schmidtbauer I, Silva FM, Pompilio CE, D'Albuquerque LA, Macedo E. Role of MELD score and serum creatinine as prognostic tools for the development of acute kidney injury after liver transplantation. *PLoS One* 2013; **8**: e64089 [PMID: 23717537 DOI: 10.1371/journal.pone.0064089]
40 **Wyssusek KH**, Keys AL, Yung J, Moloney ET, Sivalingam P, Paul SK. Evaluation of perioperative predictors of acute kidney injury post orthotopic liver transplantation. *Anaesth Intensive Care* 2015; **43**: 757-763 [PMID: 26603801 DOI: 10.1177/0310057X1504300614]
41 **Santos AM**, Seixas JM, Pereira BB, Medronho RA. Usando Redes Neurais Artificiais e Regressão Logística na predição da Hepatite A. *Revista Brasileira de Epidemiologia* 2005; **8**: 117-126
42 **Eyng E**, Fileti AMF. Control of absorption columns in the bioethanol process: Influence of measurement uncertainties. *Eng Appl Artif Intell* 2010; **23**: 271-282 [DOI: 10.1016/j.engappai.2009.11.002]
43 **Eyng E**, Silva FV, Palú F, Fileti AMF. Neural Network Based Control of an Absorption Column in the Process of Bioethanol Production. *Braz Arch Biol Techn* 2009; **52**: 961-972 [DOI: 10.1590/S1516-89132009000400020]
44 **Liew PL**, Lee YC, Lin YC, Lee TS, Lee WJ, Wang W, Chien CW. Comparison of artificial neural networks with logistic regression in prediction of gallbladder disease among obese patients. *Dig Liver Dis* 2007; **39**: 356-362 [PMID: 17317348 DOI: 10.1016/j.dld.2007.01.003]
45 **Minsky ML**, Papert SA. Perceptrons. Cambridge: MIT Press, 1969
46 **Ivanics T**, Patel MS, Erdman L, Sapisochin G. Artificial intelligence in transplantation (machine-learning classifiers and transplant oncology). *Curr Opin Organ Transplant* 2020; **25**: 426-434 [PMID: 32487887 DOI: 10.1097/MOT.0000000000000773]
47 **Kourou K**, Exarchos TP, Exarchos KP, Karamouzis MV, Fotiadis DI. Machine learning applications in cancer prognosis and prediction. *Comput Struct Biotechnol J* 2015; **13**: 8-17 [PMID: 25750696 DOI: 10.1016/j.csbj.2014.11.005]
48 **Singal AG**, Mukherjee A, Elmunzer BJ, Higgins PD, Lok AS, Zhu J, Marrero JA, Waljee AK. Machine learning algorithms outperform conventional regression models in predicting development

of hepatocellular carcinoma. *Am J Gastroenterol* 2013; **108**: 1723-1730 [PMID: 24169273 DOI: 10.1038/ajg.2013.332]

49 **Rajkomar A**, Dean J, Kohane I. Machine Learning in Medicine. *N Engl J Med* 2019; **380**: 1347-1358 [PMID: 30943338 DOI: 10.1056/NEJMra1814259]

50 **Schoenberg MB**, Bucher JN, Koch D, Börner N, Hesse S, De Toni EN, Seidensticker M, Angele MK, Klein C, Bazhin AV, Werner J, Guba MO. A novel machine learning algorithm to predict disease free survival after resection of hepatocellular carcinoma. *Ann Transl Med* 2020; **8**: 434 [PMID: 32395478 DOI: 10.21037/atm.2020.04.16]

51 **Chandra V**, Girijadevi R, Nair AS, Pillai SS, Pillai RM. MTar: a computational microRNA target prediction architecture for human transcriptome. *BMC Bioinformatics* 2010; **11** Suppl 1: S2 [PMID: 20122191 DOI: 10.1186/1471-2105-11-S1-S2]

52 **Lee HC**, Yoon SB, Yang SM, Kim WH, Ryu HG, Jung CW, Suh KS, Lee KH. Prediction of Acute Kidney Injury after Liver Transplantation: Machine Learning Approaches vs. Logistic Regression Model. *J Clin Med* 2018; **7** [PMID: 30413107 DOI: 10.3390/jcm7110428]

53 **He ZL**, Zhou JB, Liu ZK, Dong SY, Zhang YT, Shen T, Zheng SS, Xu X. Application of machine learning models for predicting acute kidney injury following donation after cardiac death liver transplantation. *Hepatobiliary Pancreat Dis Int* 2021; **20**: 222-231 [PMID: 33726966 DOI: 10.1016/j.hbpd.2021.02.001]

54 **Sendak M**, Gao M, Nichols M, Lin A, Balu S. Machine Learning in Health Care: A Critical Appraisal of Challenges and Opportunities. *EGEMS (Wash DC)* 2019; **7**: 1 [PMID: 30705919 DOI: 10.5334/egems.287]

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MINIREVIEWS

Repairing the human with artificial intelligence in oncology

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Abstract

Artificial intelligence is a groundbreaking tool to learn and analyse higher features extracted from any dataset at large scale. This ability makes it ideal to facing any complex problem that may generally arise in the biomedical domain or oncology in particular. In this work, we envisage to provide a global vision of this mathematical discipline outgrowth by linking some other related subdomains such as transfer, reinforcement or federated learning. Complementary, we also introduce the recently popular method of topological data analysis that improves the performance of learning models.

Key Words: Cancer research; Data analysis; Feature classification; Artificial intelligence; Machine learning; Healthcare systems

Core Tip: In this review, we explore powerful artificial intelligence based models enabling the comprehensive analysis of related problems on oncology. To this end, we described an asserted set of machine learning architectures that goes from the most classical multiple perceptron or neural networks to the novel federated and reinforcement learning designs. Overall, we point out the outgrowth of this mathematical discipline in cancer research and how computational biology and topological features can boost the general performances of these learning models.

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INTRODUCTION

The flourishing proliferation of artificial intelligence (AI) worldwide over the last decade has disrupted the way oncologists face cancer. More and more every day, the contribution of AI-based models to different axes of cancer research is not only improving their ability to stratify patients early on or discover new drugs but also influences its fundamentals. By integrating novel structures of data organisation, exploitation, and sharing of clinical data among health institutions, AI is achieving in the short-term to successfully accelerate cancer research. Medical practitioners are becoming familiar with some few mathematical concepts, such as machine learning (ML) or (un/semi) supervised learning. The former is a collection of data-driven techniques with the goal of building predictive models from high-dimensional datasets[1,2], while the latter refers to the grade of human intervention that these models require to make predictions.

These methods are being successfully used in cancer at many levels by simply analysing clinical data, biological indicators, or whole slide images[3-5]. Their application has revealed themselves as an effective way to tackle multiple clinical questions, from diagnosis to prediction of treatment outcomes. For instance, in Morilla *et al*[3], a minimal signature composed of seven miRNAs and two biological indicators was identified using general linear models trained at the base of a deep learning model to predict treatment outcomes in gastrointestinal cancer. In Schmauch *et al*[4], 2020, the authors predicted the RNA-Seq expression of tumours from whole slide images using a deep learning model as well.

Indeed, in this particular discipline, ML algorithms have evolved faster. Several approaches have succeeded in the classification of cancer subtypes using medical imaging[6-8]. Mammography and digital breast tomosynthesis have enabled a robust breast cancer detection by means of annotation-efficient deep learning approaches[9]. Epigenetic patterns of chromatin opening across the stem and differentiated cells across the immune system have also been predicted by deep neural networks in ATAC-seq analysis. In Maslova *et al*[10], solely from the DNA sequence of regulatory regions, the authors discovered ab initio binding motifs for known and unknown master regulators, along with their combinatorial operation.

Another domain where the application of AI-based models has largely been used is single-cell RNA sequencing (sc-RNAseq) analysis. In Lotfollahi *et al*[11] (2020), a new method based on transfer learning (TL) and parameter optimisation is introduced to enable efficient, decentralised, iterative reference building, and the contextualization of new datasets with existing single-cell references without sharing raw data. In addition, few methods have emerged around genetic perturbations of outcomes at the single-cell level in cancer treatments[12,13].

Finally, some computational topology techniques grouped under the heading of "topological data analysis" (TDA) have also been successfully proven as efficient tools in some cancer subtype classifications[14].

Thus, AI has turned the oncologists and co-workers' lives around providing them with a new perspective, which was once developed by only a bulk of specialists and is rapidly becoming a reference in the domain. This work revisits, then, most of those techniques and provides a quick overview of their applications in cancer research.

AI OR ML

ML or AI models, sometimes a philosophical matter, is a branch of mathematics concerned by numerically mimicking the human brain reasoning as it resolves a given problem. There are many examples of this practice; from those most classic techniques of regression or classification of dataset[15] to the current ground-breaking algorithms as "Deep-Mind, Alpha Fold" for protein-folding prediction[16]. In any case, all of these methods share a common objective: the ML problem. This problem can be mathematically expressed as: $$\hat{C}=\underset{C\in\mathcal{M}}{argmin}\mathbb{E}_{x,y\in\mathcal{X}\times\mathcal{Y}} [\mathcal{B}_{l} (C(x),y)]$$.

For example, if we select the particular loss function binary cross entropy, $-B_l-$, this equation describes the parameter misapplication of the neural network C by diminishing the expected value of the loss function between the output of this network $C(x)$ and the true label y.

INTERPRETABLE AI MODELS

Frequently, the intricate design of models based on any ML technique (*i.e.*, neural networks) makes them more difficult to interpret than simpler traditional models. Hence, if we want to fully exploit the potential of these models, a deeper understanding of their predictions would be advisable in practice. Thus, the predicted efficacy of a personal therapy on a cancer must be well explained, since its decisions directly influence human health. From a methodological point of view, we need to ensure model development with proper interpretations of their partial outputs in order to prevent undesirable effects of the models[17,18]. The two main streams of this discipline are the so-called "feature attribution" and "feature interaction" methods. The former[19-22] individually rewards input features depending on its local causal effect in the model output, whereas the latter examines those features with large second-order derivatives at the input or weight matrices of feed-forward and convolutional architectures[23,24]. However, the robustness of all these approaches may be compromised by the presence of specific types of architecture.

DEEP LEARNING

One class of ML models broadly used in current computational cancer research is deep neural networks. Overall, they have succeeded over other non-linear models[25] in the analysis of pathologic image recognition and later patient stratification based on the learned models[26,27]. In brief, deep neural models work in a large number of layers of information that is progressively passing by from one layer to another (*i.e.*, the backpropagation algorithms) to extract relevant features from the original data according to a non-linear model, which is associated with the selected optimisation problem. Their designs can encompass a wide range of algorithms from the classic multiple perceptron networks[28-30] and convolutional neural networks[31-36] to the most recently established long short-term memory (LSTM) recurrent neural networks (RNNs) that are put into the spotlight in the next section[37,38].

RNNs: A different and convenient design other than the more classical neural networks in which the information flows forward are the RNNs. These are computationally more complex models with the skill of capturing hidden behaviours other methods in cancer studies cannot do[39-41]. Recurrent models exhibit an intrinsic representation of the data that allows the exploitation of context information. Specifically, a recurrent network is designed to maintain information about earlier iterations for a period that depends only on the weights and input data at the model's entrance[42]. In particular, the network's activation layers take advantage of inputs that come from chains of information provided by previous iterations. This influences the current prediction and enables the gathering of network flops that can retain contextual information on a long-term scale. Thus, by following this reasoning, RNNs can dynamically exploit a contextual interval over the input training history[43].

LSTM: An improvement in of RNNs is the construction of LSTM networks. LSTMs can learn to sort the interexchange between dependencies in the predictive problems addressed by batches. These models have had a major impact on the biomedical domain, particularly in cancer research[44-48]. LSTMs have been successfully proven in analysis where the intrinsic technical drawbacks associated with RNNs have prevented a fair performance of the model[49]. There are two main optimisation problems that must be avoided during the training stage when applying LSTM to solve a problem, namely: (1) vanishing gradients; and (2) exploding gradients[50]. In this sense, LSTM specifically provides an inner structural amelioration concerning the units leveraged in the learning model[51]. However, there is an improvement in the LSTM network calibration that is increasingly used in biomedical research: LSTM bidirectional networks. In these architectures, a bidirectional recurrent neural lattice is applied in order to be able to separately pass by two forward and backward recurrent nets sharing the same output layer during the training task[51].

TL

Recycling is always a significant issue! In ML, we can also reuse a model that was originally envisaged for solving a different task other than the problem that we might

be currently facing, but both share a similar structural behaviour. This practice is called TL in ML. Its usage has been progressively increasing in problems whose architecture can consume huge amounts of time and computational resources. In these cases, pre-trained networks are applied as a starting learning point, which largely boosts the performance of new models to approach related problems. Then, TL should ameliorate the current model in another setting if such a model is available for learning features from the first problem in a general way[52,53]. Regarding its benefits in oncology, we can outstand its usage in large datasets of piled images to be recognised for patient stratification, as previously described in the following works[54-61].

REINFORCEMENT LEARNING

Reinforcement learning (RL) is one of the latest ML extensions that ameliorates the global performance of learning models when making decisions. In RL, a model learns a given objective in an a priori fixed uncertainty by means of trial and error computations until a solution is obtained. Then, to guide the model, the AI algorithm associates rewards or penalties with the local performance of the model. The final goal was to maximise the amount of rewards obtained. Remarkably, the ML architecture provides no clues on how to find the final solution, even if it rules the reward conditions. Thus, the model must smooth the optimisation problem from a totally random scenario to a complex universe of possibilities. However, if the learning algorithm is launched into a sufficiently powerful computational environment, the ML model will be able to store thousands of trials to effectively achieve the given goal. Nevertheless, a major inconvenience is that the simulation environment is highly dependent on the problem to be computed.

To sum it up, although RL should not be taken as the definitive algorithm, it promises to blow up the current concept of deep learning in oncology[62-64]. An example with no precedents is the DeepMind algorithm very famous nowadays by performing alpha protein folding[16] predictions at a scale ever done before.

FEDERATED LEARNING

A simple description of federated learning (FL) could be a decentralised approach to ML. Thus, FL boosts and accelerates medical discoveries on partnerships with many contributors while protecting patient privacy. In FL, we only improve and calibrate the results and not the data. Thus, what FL really promises it is a new era in secured AI in oncology: Training, testing, or ensuring privacy that way of learning is an efficient method of using data from a comprehensive network of resources belonging each time to a node of many interconnected hospital institutions[65-68].

TOPOLOGICAL ML

Topological ML (TML) is an interaction that has been recently established between TDA and ML. Owing to new advances in computational algorithms, the extraction of complex topological features, such as persistence homology or Betti curves, has become progressively feasible in large datasets. In particular, TDA is commonly referred to as capturing the shape of the data. This method fixes their topological invariants as hotspot to look up relevant structural and categorical information. Indeed, TDA provides ideal completeness in terms of multi-scalability and globalisation missed from the rigidness of their geometric characteristics. In that sense, the use of this tool has been growing in cancer research until it is considered as contextually informative in the analysis of massive biomedical data[69-74]. Multiple studies have exploited the complementary information that emerged from different prisms to gain new insights into the datasets. Its association with ML has enhanced both classical ML methods and deep learning models[75,76].

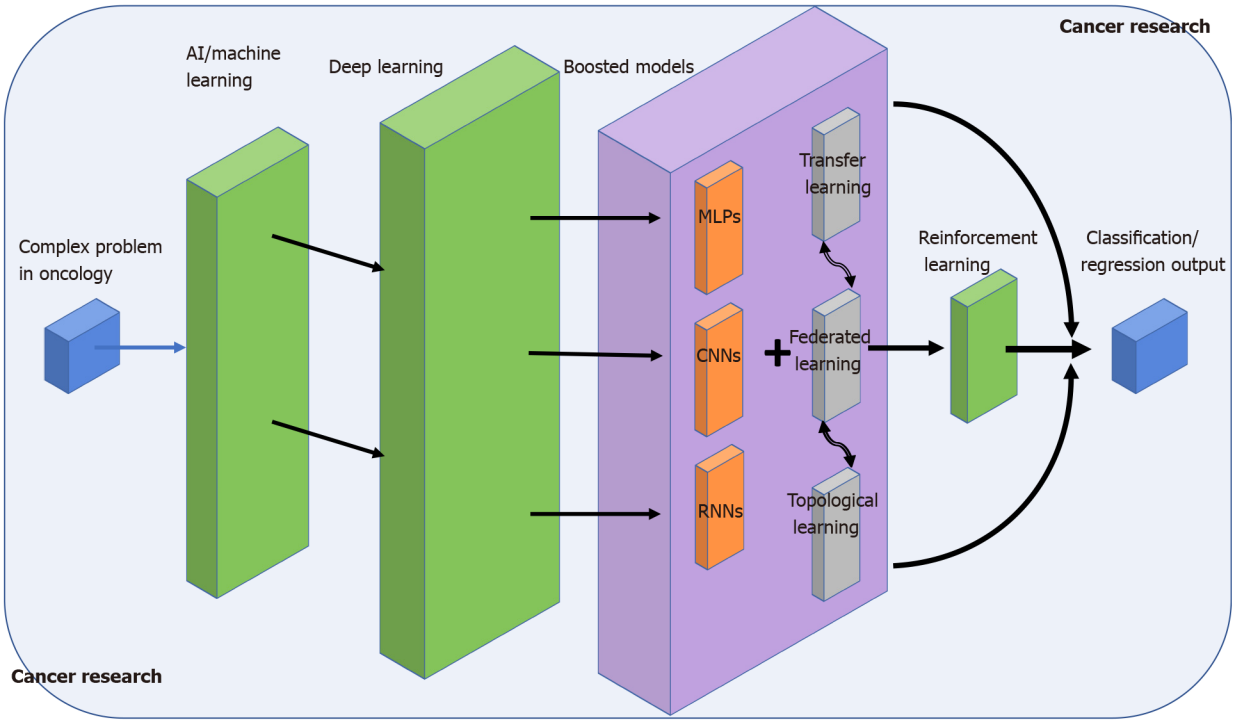

Figure 1 Relational overview of the artificial intelligence-based models introduced in this work. To solve any given complex problem in cancer research by means of machine learning models we can use many deep layers. Then, depending on the particular structures of data, we can empower the performance of the selected architecture, *i.e.*, multilayer perceptron, convolutional or recurrent networks by adding learning strategies such as transfer, federated or topological learning. These strategies are interchangeable (double banded black arrows). As well, we can directly go directly from the selected architecture to the problem's solution using reinforcement learning. AI: Artificial intelligence; MLPs: Multi-layer perceptrons; CNNs: Convolutional neural networks; RNNs: Recurrent neural networks.

CONCLUSION

In this work, we summarise the conclusions of some major references of AI in cancer research (Figure 1). Overall, we wanted to point out the rapid AI outgrowth in the biomedical domain and how AI has systematically become familiar to anyone in the domain, expert, or not. This is possibly due to recent advances in learning-oriented algorithms, which have enabled the transformation of data analysis to any scale and complexity provided a suitable environment is available. We have provided many examples of a varied set of learning models (Multi-layer perceptron, convolutional neural networks, RNNs, *etc.*) that have been successfully proven for related cancer problems such as patient stratification, image-based classification, or recording-device optimisation[77,78]. We have compared different approaches to solve similar questions, and we have introduced novel concepts such as TL, FL, or RL that prevent some of the most classical constraints regarding network architectures or information privacy on high dimensional datasets. Finally, the combination of TDA and ML has also been shown to be a promising discipline where to exploit extra topological features extracted at a higher level. Such tandem promises to contribute to the improvement of the AI algorithm's performance from a totally different perspective. Although data-driven based AI models have the potential to change the world of unsupervised learning, some limitations could endanger a promising future. The three major issues that hamper a better optimisation and general performance in AI models are related to: (1) the high dependency of the model on the data scale; (2) choice of a proper computational environment, and (3) practical problems of time or computational cost should be assumed. Thus, the future challenges in this discipline begin by smoothing such obstacles as much as possible, which will ultimately end up with AI as the tool of reference in healthcare institutions for a much broader analysis in oncology.

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REFERENCES

1 **Camacho DM**, Collins KM, Powers RK, Costello JC, Collins JJ. Next-Generation Machine Learning for Biological Networks. *Cell* 2018; **173**: 1581-1592 [PMID: 29887378 DOI: 10.1016/j.cell.2018.05.015]

2 **Morilla I**, Léger T, Marah A, Pic I, Zaag H, Ogier-Denis E. Singular manifolds of proteomic drivers to model the evolution of inflammatory bowel disease status. *Sci Rep* 2020; **10**: 19066 [PMID: 33149233 DOI: 10.1038/s41598-020-76011-7]

3 **Morilla I**, Uzzan M, Laharie D, Cazals-Hatem D, Denost Q, Daniel F, Belleannee G, Bouhnik Y, Wainrib G, Panis Y, Ogier-Denis E, Treton X. Colonic MicroRNA Profiles, Identified by a Deep Learning Algorithm, That Predict Responses to Therapy of Patients With Acute Severe Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2019; **17**: 905-913 [PMID: 30223112 DOI: 10.1016/j.cgh.2018.08.068]

4 **Schmauch B**, Romagnoni A, Pronier E, Saillard C, Maillé P, Calderaro J, Kamoun A, Sefta M, Toldo S, Zaslavskiy M, Clozel T, Moarii M, Courtiol P, Wainrib G. A deep learning model to predict RNA-Seq expression of tumours from whole slide images. *Nat Commun* 2020; **11**: 3877 [PMID: 32747659 DOI: 10.1038/s41467-020-17678-4]

5 **Saillard C**, Schmauch B, Laifa O, Moarii M, Toldo S, Zaslavskiy M, Pronier E, Laurent A, Amaddeo G, Regnault H, Sommacale D, Ziol M, Pawlotsky JM, Mulé S, Luciani A, Wainrib G, Clozel T, Courtiol P, Calderaro J. Predicting Survival After Hepatocellular Carcinoma Resection Using Deep Learning on Histological Slides. *Hepatology* 2020; **72**: 2000-2013 [PMID: 32108950 DOI: 10.1002/hep.31207]

6 **Saillard C**, Delecourt F, Schmauch B, Moindrot O, Svrcek M, Bardier-Dupas A, Emile JF, Ayadi M, De Mestier L, Hammel P, Neuzillet C, Bachet JB, Iovanna J, Nelson DJ, Paradis V, Zaslavskiy M, Kamoun A, Courtiol P, Nicolle R, Cros J. Identification of pancreatic adenocarcinoma molecular subtypes on histology slides using deep learning models. *J Clin Oncol* 2021; **39** suppl 15: 4141 [DOI: 10.1200/jco.2021.39.15_suppl.4141]

7 **Rhee S**, Seo S, Kim S. Hybrid approach of relation network and localized graph convolutional filtering for breast cancer subtype classification. In: Proceedings of the Twenty-Seventh International Joint Conference on Artificial Intelligence. International Joint Conferences on Artificial Intelligence Organization, 2018: 3527–3534 [DOI: 10.24963/ijcai.2018/490]

8 **Schutte K**, Moindrot O, Hérent P, Schiratti JB, Jégou S. Using stylegan for visual interpretability of deep learning models on medical images. 2021 Preprint. Available from: ArXiv:2101.07563

9 **Lotter W**, Diab AR, Haslam B, Kim JG, Grisot G, Wu E, Wu K, Onieva JO, Boyer Y, Boxerman JL, Wang M, Bandler M, Vijayaraghavan GR, Gregory Sorensen A. Robust breast cancer detection in mammography and digital breast tomosynthesis using an annotation-efficient deep learning approach. *Nat Med* 2021; **27**: 244-249 [PMID: 33432172 DOI: 10.1038/s41591-020-01174-9]

10 **Maslova A**, Ramirez RN, Ma K, Schmutz H, Wang C, Fox C, Ng B, Benoist C, Mostafavi S; Immunological Genome Project. Deep learning of immune cell differentiation. *Proc Natl Acad Sci U S A* 2020; **117**: 25655-25666 [PMID: 32978299 DOI: 10.1073/pnas.2011795117]

11 **Lotfollahi M**, Naghipourfar M, Luecken MD, Khajavi M, Uttner MB, Avsec Z, Misharin AV, Theis FJ. Query to reference singlecell integration with transfer learning. 2020 Preprint. Available from: bioRxiv:2020.07.16.205997 [DOI: 10.1101/2020.07.16.205997]

12 **Hou W**, Ji Z, Ji H, Hicks SC. A systematic evaluation of single-cell RNA-sequencing imputation methods. *Genome Biol* 2020; **21**: 218 [PMID: 32854757 DOI: 10.1186/s13059-020-02132-x]

13 **Zhang Y**, Wang D, Peng M, Tang L, Ouyang J, Xiong F, Guo C, Tang Y, Zhou Y, Liao Q, Wu X, Wang H, Yu J, Li Y, Li X, Li G, Zeng Z, Tan Y, Xiong W. Single-cell RNA sequencing in cancer research. *J Exp Clin Cancer Res* 2021; **40**: 81 [PMID: 33648534 DOI: 10.1186/s13046-021-01874-1]

14 **Dindin M**, Umeda Y, Chazal F. Topological data analysis for arrhythmia detection through modular neural networks. In: Goutte C, Zhu X, editors. Advances in Artificial Intelligence. Cham: Springer International Publishing, 2020: 177-188 [DOI: 10.1007/978-3-030-47358-7_17]

15 **Azzaoui T**, Santos D, Sheikh H, Lim S. Solving classification and regression problems using machine and deep learning. Technical report, University of Massachusetts Lowell, 2018 [DOI: 10.13140/RG.2.2.21723.21288]

16 **Deepmind**. Deepmind alphafolding. [Accessed: 2021-10-12] Available from: https://deepmind.com/research

17 **Sundararajan M**, Taly A, Yan Q. Axiomatic attribution for deep networks. In: ICML'17: Proceedings of the 34th International Conference on Machine Learning - Volume 70. JMLR.org, 2017: 3319–3328

18 **Janizek JD**, Sturmfels P, Lee SI. Explaining explanations: Axiomatic feature interactions for deep networks. *J Mach Learn Res* 2021; **22**: 1-54

19 **Binder A**, Montavon G, Lapuschkin S, Muller KR, Same W. Layer-wise relevance propagation for neural networks with local renormalization layers. In: Villa A, Masulli P, Pons Rivero A, editors. Artificial Neural Networks and Machine Learning – ICANN 2016. ICANN 2016. Lecture Notes in Computer Science, vol 9887. Cham: Springer, 2016: 63-71 [DOI: 10.1007/978-3-319-44781-0_8]

20 **Ribeiro MT**, Singh S, Guestrin C. "why should i trust you?" explaining the predictions of any classifier. In: KDD'16: Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining. New York: Association for Computing Machinery, 2016: 1135–1144 [DOI: 10.1145/2939672.2939778]

21 **Shirkumar A**, Greenside P, Kundaje A. Learning important features through propagating activation diferences. In: Precup D, Teh YW, editors. Proceedings of the 34th International Conference on Machine Learning. JMLR org, 2017: 3145–3153

22 **Lundeberg SM**, Lee SI. A unified approach to interpreting model predictions. In: Proceedings of the 31st International Conference on Neural Information Processing Systems (NIPS'17). Red Hook: Curran Associates Inc., 2017: 4768-4777

23 **Cui T**, Marttinen P, Kaski S. Recovering pairwise interactions using neural networks. 2019 Preprint. Available from: arXiv:1901.08361

24 **Greenside P**, Shimko T, Fordyce P, Kundaje A. Discovering epistatic feature interactions from neural network models of regulatory DNA sequences. *Bioinformatics* 2018; **34**: i629-i637 [PMID: 30423062 DOI: 10.1093/bioinformatics/bty575]

25 **Shavitt I**, Segal E. Regularization learning networks: Deep learning for tabular datasets. In: Bengio S, Wallach H, Larochelle H, Grauman K, Cesa-Bianchi N, Garnett R, editors. Advances in Neural Information Processing Systems, volume 31. Red Hook: Curran Associates Inc., 2018 [DOI: 10.7551/mitpress/7503.003.0107]

26 **Devlin J**, Chang MW, Lee K, Toutanova K. Bert: Pre-training of deep bidirectional transformers for language understanding. In: Proceedings of the 2019 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies, Volume 1 (Long and Short Papers). Minneapolis: Association for Computational Linguistics, 2019: 4171-4186 [DOI: 10.18653/v1/n19-1423]

27 **He K**, Zhang X, Ren S, Sun J. Deep residual learning for image recognition. 2015 Preprint. Available from: arXiv:1512.03385

28 **Kumar G**, Pawar U, O'Reilly R. Arrhythmia detection in ECG signals using a multilayer perceptron network. In: Curry E, Keane MT, Ojo A, Salwala D, editors. AICS, volume 2563 of CEUR Workshop Proceedings. CEUR-WS.org, 2019: 353-364

29 **Alsmadi MK**, Omar KB, Noah SA, Almarashdah I. Performance comparison of multi-layer perceptron (back propagation, delta rule and perceptron) algorithms in neural networks. In: 2009 IEEE International Advance Computing Conference. IEEE, 2009: 296–299 [DOI: 10.1109/iadcc.2009.4809024]

30 **Freund Y**, Schapire RE. Large margin classification using the perceptron algorithm. *Mach Learn* 1999; **37**: 277-296 [DOI: 10.1023/A:1007662407062]

31 **Hadush S**, Girmay Y, Sinamo A, Hagos G. Breast cancer detection using convolutional neural networks. 2020 Preprint. Available from: arXiv:2003.07911

32 **Chaturvedi SS**, Tembhurne JV, Diwan T. A multi-class skin cancer classification using deep convolutional neural networks. *Multim Tools Appl* 2020; 28477-27498 [DOI: 10.1007/s11042-020-09388-2]

33 **Santos C**, Afonso L, Pereira C, Papa J. BreastNet: Breast cancer categorization using convolutional neural networks. In: 2020 IEEE 33rd International Symposium on Computer-Based Medical Systems (CBMS). IEEE, 2020: 463-468 [DOI: 10.1109/CBMS49503.2020.00094]

34 **Yoo S**, Gujrathi I, Haider MA, Khalvati F. Prostate Cancer Detection using Deep Convolutional Neural Networks. *Sci Rep* 2019; **9**: 19518 [PMID: 31863034 DOI: 10.1038/s41598-019-55972-4]

35 **Kumar N**, Verma R, Arora A, Kumar A, Gupta S, Sethi S, Gann PH. Convolutional neural networks for prostate cancer recurrence prediction. In: Gurcan MN, Tomaszewski JE, editors. Proceedings Volume 10140, Medical Imaging 2017: Digital Pathology. SPIE, 2017: 101400H [DOI: 10.1117/12.2255774]

36 **Dumoulin V**, Francesco V. A guide to convolution arithmetic for deep learning. 2016 Preprint. Available from: arXiv:1603.07285

37 **Graves A**. Long Short-Term Memory. Berlin: Springer Berlin Heidelberg 2012; 37-45 [DOI: 10.1007/978-3-642-24797-2_4]

38 **Hochreiter S**, Schmidhuber J. Long short-term memory. *Neural Comput* 1997; **9**: 1735-1780 [PMID: 9377276 DOI: 10.1162/neco.1997.9.8.1735]

39 **Lane N**, Kahanda I. DeepACPpred: A Novel Hybrid CNN-RNN Architecture for Predicting Anti-Cancer Peptides. In: Panuccio G, Rocha M, Fdez-Riverola F, Mohamad MS, Casado-Vara R, editors. PACBB, volume 1240 of Advances in Intelligent Systems and Computing. Springer, 2020: 60-69 [DOI: 10.1007/978-3-030-54568-0_7]

40 **Moitra D**, Mandal RK. Automated AJCC (7th edition) staging of non-small cell lung cancer (NSCLC) using deep convolutional neural network (CNN) and recurrent neural network (RNN). *Health Inf Sci Syst* 2019; **7**: 14 [PMID: 31406570 DOI: 10.1007/s13755-019-0077-1]

41 **Chiang JH**, Chao SY. Modeling human cancer-related regulatory modules by GA-RNN hybrid algorithms. *BMC Bioinformatics* 2007; **8**: 91 [PMID: 17359522 DOI: 10.1186/1471-2105-8-91]

42 **Bengio Y**, Simard P, Frasconi P. Learning long-term dependencies with gradient descent is difficult. *IEEE Trans Neural Netw* 1994; **5**: 157-166 [PMID: 18267787 DOI: 10.1109/72.279181]

43 **Sak H**, Senior AW, Beaufays F. Long short-term memory recurrent neural network architectures for large scale acoustic modeling. In: Li H, Meng HM, Ma B, Chng E, Xie L, editors. Proc. Interspeech 2014. ISCA, 2014: 338–342 [DOI: 10.21437/Interspeech.2014-80]

44 **Agrawal P**, Bhagat D, Mahalwal M, Sharma N, Raghava GPS. AntiCP 2.0: an updated model for predicting anticancer peptides. *Brief Bioinform* 2021; **22** [PMID: 32770192 DOI: 10.1093/bib/bbaa153]

45 **Jiang L**, Sun X, Mercaldo F, Antonella Santone A. Decablstm: Deep contextualized attentional bidirectional lstm for cancer hallmark classification. *Knowl Based Syst* 2020; **210**: 106486 [DOI: 10.1016/j.knosys.2020.106486]

46 **Asyhar AH**, Foeady AZ, Thohir M, Arifin AZ, Haq DZ, Novitasari DCR. Implementation LSTM Algorithm for Cervical Cancer using Colposcopy Data. In: 2020 International Conference on Artificial Intelligence in Information and Communication (ICAIIC). IEEE, 2020: 485-489 [DOI: 10.1109/icaiic48513.2020.9065068]

47 **Bichindaritz I**, Liu G, Bartlett CL. Survival prediction of breast cancer patient from gene methylation data with deep LSTM network and ordinal cox model. In: Bartk R, Bell E, editors. FLAIRS Conference. AAAI Press, 2020: 353–356 [DOI: 10.32473/flairs.v34i1.128570]

48 **Gao R**, Huo Y, Bao S, Tang Y, Antic S, Epstein ES, Balar A, Deppen S, Paulson AB, Sandler KL, Massion PP, Landman BA. Distanced LSTM: Time-distanced gates in long short-term memory models for lung cancer detection. In: Suk HI, Liu M, Yan P, Lian C, editors. Machine Learning in Medical Imaging. MLMI 2019. Lecture Notes in Computer Science, vol 11861. Cham: Springer, 2019: 310-318 [DOI: 10.1007/978-3-030-32692-0_36]

49 **Gers FA**, Schmidhuber J, Cummins F. Learning to forget: continual prediction with LSTM. *Neural Comput* 2000; **12**: 2451-2471 [PMID: 11032042 DOI: 10.1162/089976600300015015]

50 **Graves A**, Liwicki M, Fernández S, Bertolami R, Bunke H, Schmidhuber J. A novel connectionist system for unconstrained handwriting recognition. *IEEE Trans Pattern Anal Mach Intell* 2009; **31**: 855-868 [PMID: 19299860 DOI: 10.1109/TPAMI.2008.137]

51 **Graves A**, Schmidhuber J. Framewise phoneme classification with bidirectional LSTM and other neural network architectures. *Neural Netw* 2005; **18**: 602-610 [PMID: 16112549 DOI: 10.1016/j.neunet.2005.06.042]

52 **Olivas ES**, Guerrero JDM, Sober MM, Benedito JRM, Lopez AJS. Handbook Of Research On Machine Learning Applications and Trends: Algorithms, Methods and Techniques - 2 Volumes. Hershey: IGI Publishing, 2009 [DOI: 10.4018/978-1-60566-766-9]

53 **Yosinski J**, Clune J, Bengio Y, Lipson H. How transferable are features in deep neural networks? In: NIPS'14: Proceedings of the 27th International Conference on Neural Information Processing Systems - Volume 2. Cambridge: MIT Press, 2014: 3320-3328

54 **Khamparia A**, Bharati S, Podder P, Gupta D, Khanna A, Phung TK, Thanh DNH. Diagnosis of breast cancer based on modern mammography using hybrid transfer learning. *Multidimens Syst Signal Process* 2021; 1-19 [PMID: 33456204 DOI: 10.1007/s11045-020-00756-7]

55 **Jayachandran S**, Ghosh A. Deep transfer learning for texture classification in colorectal cancer histology. In: Schilling FP, Stadelmann T, editors. Artificial Neural Networks in Pattern Recognition. ANNPR 2020. Lecture Notes in Computer Science, vol 12294. Cham: Springer, 2020: 173-186 [DOI: 10.1007/978-3-030-58309-5_14]

56 **Shaikh TA**, Ali R, Sufyan Beg MM. Transfer learning privileged information fuels CAD diagnosis of breast cancer. *Mach Vis Appl* 2020; **31**: 9 [DOI: 10.1007/s00138-020-01058-5]

57 **de Matos J**, de Souza Britto A, Oliveira LES, Koerich AL. Double transfer learning for breast cancer histopathologic image classification. In: 2019 International Joint Conference on Neural Networks (IJCNN). IEEE, 2019: 1-8 [DOI: 10.1109/IJCNN.2019.8852092]

58 **Obonyo S**, Ruiru D. Multitask learning or transfer learning? application to cancer detection. In: Merelo JJ, Garibaldi JM, Linares-Barranco A, Madani K, Warwick K, editors. Computational Intelligence. ScitePress, 2019: 548–555

59 **Kassani SH**, Kassani PH, Wesolowski MJ, Schneider KA, Deters R. Breast cancer diagnosis with transfer learning and global pooling. In: 2019 International Conference on Information and Communication Technology Convergence (ICTC). IEEE, 2019: 519-524 [DOI: 10.1109/ICTC46691.2019.8939878]

60 **Dhruba SR**, Rahman R, Matlock K, Ghosh S, Pal R. Application of transfer learning for cancer drug sensitivity prediction. *BMC Bioinformatics* 2018; **19**: 497 [PMID: 30591023 DOI: 10.1186/s12859-018-2465-y]

61 **Vesal S**, Ravikumar N, Davari A, Ellmann S, Maier AK. Classification of breast cancer histology images using transfer learning. In: Campilho A, Karray F, ter Haar Romeny B, editors. Image Analysis and Recognition. ICIAR 2018. Lecture Notes in Computer Science, vol 10882. Cham: Springer, 2018: 812–819 [DOI: 10.1007/978-3-319-93000-8_92]

62 **Kalantari J**, Nelson H, Chia N. The Unreasonable Effectiveness of Inverse Reinforcement Learning in Advancing Cancer Research. *Proc Conf AAAI Artif Intell* 2020; **34**: 437-445 [PMID: 34055465 DOI: 10.1609/aaai.v34i01.5380]

63 **Daoud S**, Mdhaffar A, Jmaiel M, Freisleben B. Q-Rank: Reinforcement Learning for Recommending Algorithms to Predict Drug Sensitivity to Cancer Therapy. *IEEE J Biomed Health Inform* 2020; **24**: 3154-3161 [PMID: 32750950 DOI: 10.1109/JBHI.2020.3004663]

64 **Balaprakash P**, Egele R, Salim M, Wild S, Vishwanath V, Xia F, Brettin T, Stevens R. Scalable reinforcement-learning-based neural architecture search for cancer deep learning research. In: Proceedings of the International Conference for High Performance Computing, Networking, Storage and Analysis. New York: Association for Computing Machinery, 2019: 1-33 [DOI: 10.1145/3295500.3356202]

65 **Beguier C**, Andreux M, Tramel EW. Efficient Sparse Secure Aggregation for Federated Learning. 2020 Preprint. Available from: arXiv:2007.14861

66 **Andreux M**, du Terrail JO, Beguier C, Tramel EW. Siloed federated learning for multi-centric histopathology datasets. 2020 Preprint. Available from: arXiv:2008.07424

67 **Andreux M**, Manoel A, Menuet R, Saillard C, Simpson C. Federated Survival Analysis with Discrete-Time Cox Models. 2020 Preprint. Available from: arXiv:2006.08997

68 **Rieke N**, Hancox J, Li W, Milletarì F, Roth HR, Albarqouni S, Bakas S, Galtier MN, Landman BA, Maier-Hein K, Ourselin S, Sheller M, Summers RM, Trask A, Xu D, Baust M, Cardoso MJ. The future of digital health with federated learning. *NPJ Digit Med* 2020; **3**: 119 [PMID: 33015372 DOI: 10.1038/s41746-020-00323-1]

69 **Hensel F**, Moor M, Rieck B. A Survey of Topological Machine Learning Methods. *Front Artif Intell* 2021; **4**: 681108 [PMID: 34124648 DOI: 10.3389/frai.2021.681108]

70 **Groha S**, Weis C, Gusev A, Rieck B. Topological data analysis of copy number alterations in cancer. 2020 Preprint. Available from: arXiv:2011.11070

71 **Loughrey C**, Fitzpatrick P, Orr N, Jurek-Loughrey A. The topology of data: Opportunities for cancer research. *Bioinformatics* 2021 [PMID: 34320632 DOI: 10.1093/bioinformatics/btab553]

72 **Gonzalez G**, Ushakova A, Sazdanovic R, Arsuaga J. Prediction in Cancer Genomics Using Topological Signatures and Machine Learning. In: Baas N, Carlsson G, Quick G, Szymik M, Thaule M, editors. Topological Data Analysis. Abel Symposia. Cham: Springer, 2020: 247-276 [DOI: 10.1007/978-3-030-43408-3_10]

73 **Yu YT**, Lin GH, Jiang IHR, Chiang CC. Machine learning-based hotspot detection using topological classification and critical feature extraction. *IEEE Trans Comput Aided Des Integr Circuits Syst* 2015; **34**: 460-470 [DOI: 10.1109/TCAD.2014.2387858]

74 **Matsumoto T**, Kitazawa M, Kohno Y. Classifying topological charge in SU(3) YangMills theory with machine learning. *Prog Theor Exp Phys* 2021; **2**: 023D01 [DOI: 10.1093/ptep/ptaa138]

75 **Bukkuri A**, Andor N, Darcy IK. Applications of Topological Data Analysis in Oncology. *Front Artif Intell* 2021; **4**: 659037 [PMID: 33928240 DOI: 10.3389/frai.2021.659037]

76 **Huang CH**, Chang PM, Hsu CW, Huang CY, Ng KL. Drug repositioning for non-small cell lung cancer by using machine learning algorithms and topological graph theory. *BMC Bioinformatics* 2016; **17** Suppl 1: 2 [PMID: 26817825 DOI: 10.1186/s12859-015-0845-0]

77 **Morilla I**. A deep learning approach to evaluate intestinal fibrosis in magnetic resonance imaging models. *Neural Comput Appl* 2020; **32**: 14865-14874 [DOI: 10.1007/s00521-020-04838-2]

78 **Morilla I**, Uzzan M, Cazals-Hatem D, Colnot N, Panis Y, Nancey S, Boschetti G, Amiot A, Tréton X, Ogier-Denis E, Daniel F. Computational Learning of microRNA-Based Prediction of Pouchitis Outcome After Restorative Proctocolectomy in Patients With Ulcerative Colitis. *Inflamm Bowel Dis* 2021; **27**: 1653-1660 [PMID: 33609036 DOI: 10.1093/ibd/izab030]

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MINIREVIEWS

Artificial intelligence reveals roles of gut microbiota in driving human colorectal cancer evolution

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Abstract

With the rapid development of high-throughput sequencing and artificial intelligence (AI) techniques, gut mucosal microbiota begins to be recognized as critical drivers of human colorectal cancer (CRC). Various AI approaches have been designed to obtain effective information from enormous numbers of microbial cells residing in gut mucosal as well as cancer cells. These mainly include detection of microbial markers for early clinical diagnosis of stage-specific CRC, characterization of pathogenic bacterial activities *via* genomic and transcriptomic analyses, and prediction of interplay between bacterial drivers and host immune systems. Here I review the current progresses of AI applications in profiling gut microbiomes linked to CRC initiation and development. I further look forward to future AI research for improving our understanding of the roles of gut microbiota in CRC evolution.

Key Words: Artificial intelligence; Colorectal cancer; Gut microbiome; High-throughput sequencing

Core Tip: In this review, the author reviews the current progresses of artificial intelligence (AI) applications in profiling gut microbiomes linked to colorectal cancer (CRC) initiation and development. The author further looks forward to future AI research for improving our understanding of the roles of gut microbiota in CRC evolution.

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INTRODUCTION

Colorectal cancer (CRC) continuously receives public and academic attentions due to its high prevalence and mortality rate[1]. Understanding the genetic mechanisms behind CRC initiation and progression is important to the development of early diagnosis and new therapy for CRC and its recurrence. The concept of the adenoma-carcinoma sequence, which refers to a sequential activation of oncogenes and inactivation of tumor suppressor genes, is well recognized for CRC progression[2,3]. The adenoma-carcinoma sequence involves genetic mutations and epigenetic modification of human genome in vivo, which have been believed to be caused by exogenous and endogenous mutagens for decades[4-6]. However, it is still not fully understood which exogenous mutagens induce cancers and the induction mechanisms behind them remain largely unknown, especially when the questions go deep to a defined type of cancer.

Growing evidences indicate that gut mucosal microbiota is strongly linked to CRC development and may serve as a primary driver to induce inflammation in the human colon[7-13]. High-throughput sequencing (HTS) of 16S ribosomal RNA (rRNA) gene fragments is widely applied to profile microbial communities and used to study the composition structures of gut mucosal microbiota associated with human CRC (Figure 1)[14-17]. Moreover, metagenome sequencing of gut mucosal microbiomes coupled with binning strategies and other downstream analysis are able to reveal metabolism pathways in potential pathogenic bacteria at lineage levels, which are critical to screening microbial biomarkers (*e.g.*, taxa and gene) for CRC and understanding the microbe-host interactions (Figure 1)[18-20]. Emerging meta transcriptomic sequencing, which examines large-scale gene expressions in microbial communities, is able to provide comprehensive insights into microbial population activities in host. Based on these in silico analyses and following wet-lab validations, species such as *Fusobacterium nucleatum*, *Peptostreptococcus anaerobius*, pks$^+$ *Escherichia coli* and *Eubacterium rectale* have been identified as pathogenic drivers responsible for CRC progression[9,10,12,21]. However, due to the expensive and time-consuming wet-lab experiments, a list of CRC-associated species is on the way to be examined for the physiological roles in CRC progression. Instead, AI approaches can serve as efficient methods to detect potential roles of these microbes in microbe-host interactions and provide clues for wet-lab validation.

With its increasingly wide applications in our everyday life, *e.g.* self-driving cars, facial recognition, and medical diagnosis, AI becomes one of the most popular fields that are heavily invested and supported in a number of countries. AI is capable of mimicking and going beyond human capabilities. In some biological fields such as genomics and transcriptomics, AI is able to complete the complex tasks that are impossible for human to finish[22]. AI technique encompasses machine learning (ML) as a major branch that includes deep learning as a subset of ML[23,24]. In essence, ML are computing algorithms that are either supervised by training datasets or designed as unsupervised algorithms. They are widely applied in gut microbiome field. Here I review the current progresses of AI applications in detection of pathogenic drivers for CRC and prediction of their driving roles in CRC evolution.

TAXONOMIC PROFILING OF GUT MICROBIOMES BASED ON 16S RRNA GENE SEQUENCING

Classification algorithms to categorize operational taxonomic unit

To understand the roles of pathogenic bacterial species in initiating and driving CRC progression, the first and most important step is to identify the spectrum of indigenous bacterial taxonomy in human gut. Current HTS technology has developed sufficiently mature methods and is able to extensively characterize bacterial taxonomy in samples collected from diverse environments and various hosts, including human gut mucosal[14-20,25,26]. As a key step for taxonomic assignment, classification of operational taxonomic units (OTUs) from large datasets of HTS 16S rRNA sequencing reads employs various AI algorithms. Classical algorithms for OTU classification include long-sequence-fist list removal algorithm[27,28], uclust algorithm[29], random

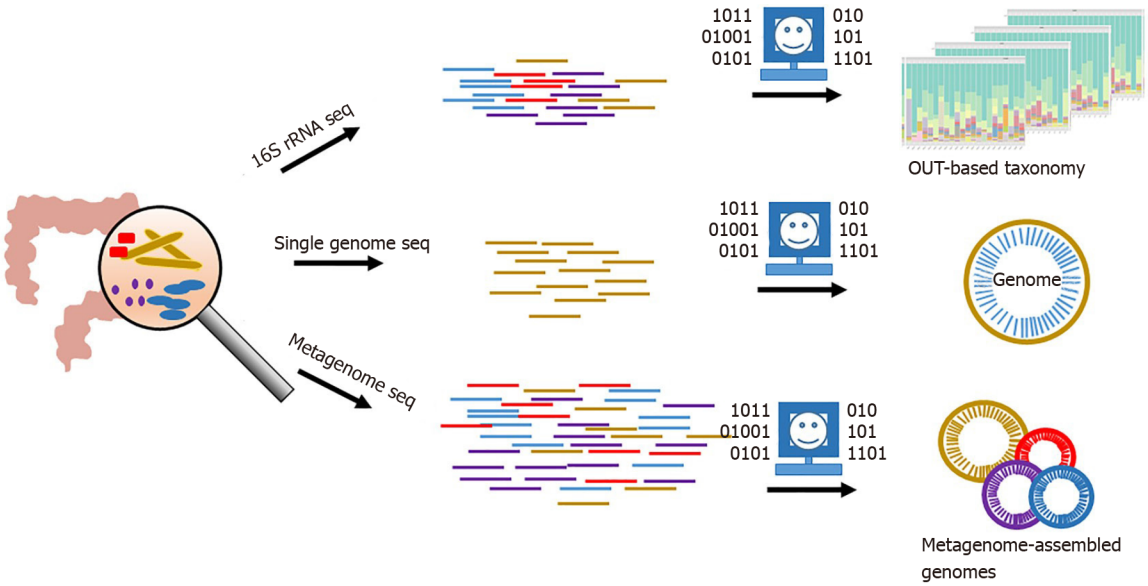

Figure 1 Schematic of artificial intelligence applications in characterizing the traits of gut microbiota associated with colorectal cancer.
OTU: Operational taxonomic unit.

forest algorithm[30], and RDP naïve Bayesian classifier algorithm[31]. Because the datasets are usually generated in large scales, both accuracy and computation speed must be considered for trade off. Long-sequence-fist list removal algorithm implements a super-fast heuristic to identity DNA segments with high identity between sequences, to avoid costly computational alignments of full sequences[27,28]. Uclust algorithm sorts k-mer of sequencing reads to rapidly identify sequences in common[29]. Random forest algorithm builds an ensemble of decision trees that are trained with a combination of learning models[30]. RDP naïve Bayesian classifier algorithm classifies based on the multinomial model in both training and testing for computing classification probabilities[31]. However, challenges still remain to accurately determine the species using 16S rRNA sequences. Errors introduced due to experimental limitations such as polymerase chain reaction amplification and HTS sequencing need to be considered. In addition, although hypervariable regions in 16S rRNA sequences were used for taxonomic assignment, some sequences from bacterial species within the same genus are highly homologous or identical, leading to problems for taxonomic assignment. To solve these issues, new algorithms are also developed. For example, Bayesian-like operational taxonomic unit examiner algorithm employs a grammar-based assignment strategy to deal with sequencing reads errors, in which unsupervised Bayesian models are built based on k-mers split from sequencing reads[32]. To solve homology issues of hypervariable regions in 16S rRNA, Gwak and Rho used a k-nearest neighbor algorithm and the species consensus sequence models to determine species-level taxonomy[33]. Further development of AI methods for OTU classification will help improve the accuracy for taxonomic assignment and speed for dealing with large-scale dataset.

Neighbor-joining and maximum-likelihood based phylogenetic trees

Since gut microbiome OTUs may represent novel species/strains, placing them on a phylogenetic tree can shed light on their taxonomic positions. The computation of phylogenetic likelihood for reconstruction of evolutionary tress from sequence data is both memory and computing consuming. Both Neighbor-Joining (NJ) and maximum-likelihood algorithms are the most popular methods in resolving topology of OTU sequences[34-38]. The NJ tree inference method belongs to distance-based method and takes a matrix of pairwise distance between the sequences to build evolutionary tree. The maximum-likelihood algorithm calculates all the possible tree topologies based on the probability.

Principal component analysis based dimension reduction of big data

The composition structure of gut microbiome is highly complex, containing high-dimensional information for hundreds of bacterial species and their abundances[39]. To apply data mining strategies on looking for critical factors that distinguish gut

microbiomes, large numbers of samples were usually collected from patients in different CRC conditions, such as various intestinal locations and CRC stages. To examine the differences among samples that belong to specific conditions, the high-dimensional information from each sample need to be reduced and presented on a two-dimensional space. As an unsupervised algorithm, principal component analysis is a dimensionality reduction algorithm that transforms and compresses matrix consisting of high-dimensional interrelated variables to a new set of two-dimensional variables[40,41]. By plotting the compressed two-dimensional variables, the microbiome patterns of gut mucosal samples collected from different conditions can be evaluated.

CLINICAL MICROBIAL GENOMIC ASSEMBLY ALGORITHM

To understand gut microbiome functions, bacteria residing in gut mucosal ecosystem need to be isolated and cultivated in laboratory for experimental validation[42]. Sequencing the genomes of these bacteria can reveal their metabolism traits and guide downstream functional analyses. For whole genome shotgun sequencing, bacterial genomic DNA is fragmented into small pieces for 2 × 100 or 2 × 150 bp paired-end sequencing. Various de novo assemblers, including Velvet, SPAdes and SoapDeNovo, have been designed to assemble a large number of short sequence reads to form a set of contiguous sequences representing the genome[43-45]. Because the reads are short, they are usually generated in large quantities with a high coverage depth. To deal with such a large dataset, the assemblers are not designed to assemble the short reads directly. Instead, the reads are splitted to form a set of k-mers and then mapped through de Bruijn graph. Although de Bruijn graph is suggested for short read assembly (100-200 bp), it is not recommended to assemble very short reads (25-50 bp). Velvet was designed to manipulate de Bruijn graph algorithm efficiently for very short reads assembly[43]. Elimination of errors and resolving repeats regions were considered in Velvet[43]. Reconstruction of consensus sequences from k-mers based on de Bruijn algorithm may lead to fragmented assembly. To deal with the issues, paired de Bruijn graphs using read-pairs (bireads) was designed. Inspired by paired de Bruijn graphs, SPAdes uses paired assembly graph algorithm by introducing k-bimer adjustment that reveals exact distances for the adjusted k-bimers[44]. SOAPdevo2, as the version 2 of SOAPdenovo, also utilizes de Bruijn graph algorithm but is designed to reduce memory consumption in de Bruijn graph constructions[45]. The algorithm supports error correction for long k-mers to improve accuracy and sensitivity during the assembly process. Moreover, the program benefits the assembly of repeat regions with high coverage depth and regions with low coverage depth *via* application of a k-mer size selection strategy. Therefore, these assembly algorithms have their specific advantages and are widely utilized in practical applications.

METAGENOMICS ASSEMBLY AND BINNING

Gut mucosal microbiomes comprise hundreds of bacterial species, of which some are uncultivable in laboratory conditions[46,47]. Sequencing these mixed bacterial populations facilitates discovery of the genomic traits of these uncultivable bacteria. Although assembling the reads and reconstructing genes from these complex mixtures are challenging, metagenomic assembly algorithms and downstream binning strategies are under developing progresses to solve the technique problems.

Metagenomic assembly algorithms

Genome assembly for sequencing reads from a single species assumes that all the reads are sequenced from the same genomic DNA and contaminations can be screened out during quality control process[48]. The genome size of single species can be estimated based on the sizes of close phylogenetic neighbors and k-mer counting, and the required sequencing depth can be calculated according to the genome size. During assembly process, de Bruijn algorithm is designed to simply consider nodes or edges with low coverage depth as contamination and remove them[48,49]. In the same way, nodes with high coverage depth are considered by the algorithm as repetitive regions in the genome sequence. In contrast, metagenomic assembly cannot make such a simple assumption to decide nodes with low and high coverage depths to be from contamination sequences or repetitive regions. This is because metagenomic

sequencing reads are generated from mixed bacterial populations, in which certain species grow better than the rest and show high abundances in the mixed communities, whereas rare species show low abundances. Therefore, the coverage depths of heterogeneous reads cannot facilitate the assumption of their origins.

Currently, the most popular assemblers for metagenomics assembly include MEGAHIT and metaSPAdes[50,51]. MEGAHIT utilizes a fast parallel algorithm for succinct de Bruijn graphs to assemble k-mers from metagenomics reads[50]. To avoid k-mer singletons caused by sequencing error, MEGAHIT sorts and counts all (k + 1)-mers splitted from the sequencing reads and only counts (k + 1)-mers with > 2 occurrences[50]. In addition, MEGAHIT utilizes a mercy-kmers strategy to recover low-depth edges for the assembly of rare species[50]. MetaSPAdes uses de Bruijn graph of all reads using SPAdes, transforms it into the assembly graph using various simplification procedures[51]. The algorithm works across a wide range of coverage depths.

Binning strategy

Since assembled metagenomic scaffolds/contigs are derived from each species and show sequence composition characteristics such as GC content and coverage depth, various binning strategies are designed for the reconstruction of metagenome-assembled genome (MAG). MAGs represent genomes from monophyletic lineages and can be used to analyze taxonomic and metabolic potentials. A number of programs have been designed for MAG binning, including MetaBat2, Maxbin2, CONCOCT, MyCC, and BinSanity[52-56]. MetaBat2 is a user-friendly program that does not need to tune the parameters for its sensitivity and specificity[52]. It utilizes a new adaptive binning algorithm to tune these parameters automatically, and uses a graph based structure for contig clustering. MetaBat2 is optimized for extensive low-level computation and works very efficiently for very large datasets. MaxBin 2.0 employs an Expectation-Maximization algorithm to recover draft genomes from metagenomes [53]. It measures the tetranucleotide frequencies of the contigs and their coverages and then classifies the contigs into each bins. CONCOCT uses Gaussian mixture models to cluster contigs into bins[54]. Sequence composition and coverage are considered for assigning contigs to bins. A variational Bayesian approach is used to determine the number of clusters. MyCC works in a way using metagenomics signatures, contig/scaffold coverage depths, and Barnes-Hut-SNE-based dimension reduction [55]. MyCC predicts genes in metagenomic contigs using Prodigal and then identifies single-copy marker genes using Hidden Markov Model trained FetchMG along with UCLUST. The reduced genomic signatures *via* Barnes-Hut-SNE algorithm are then clustered using affinity propagation for binning. Similarly, BinSanity utilizes affinity propagation algorithm to generate bins based on coverage depth, tetranucleotide frequency, and GC content[56]. Although these bin extraction algorithms are designed based on their own specific principles, the resulted bins from the same dataset can be combined, evaluated, modified, and improved to generate high-quality final set of bins using metaWRAP[57].

Quality checking and taxonomic inference for MAGs

Quality evaluation of the assembled MAGs determines the reliability of downstream annotation analyses. Because the concept of metagenome sequencing is quite new, not many programs have been developed with matured principles to determine MAG qualities. Currently, the most popular program is CheckM, which uses a set of lineage-specific marker genes within a reference genome tree[58]. By this way, CheckM estimates the completeness and contamination of the assembled MAGs and determines which MAGs are useful for downstream analyses. To determine the set of marker genes, CheckM reconstructed a genome tree based on 5656 reference genomes and then inferred the marker gene set using HMMER based on hidden Markov models and FastTree based on WAG and GAMMA models. To evaluate a MAG, the marker gene set is identified in the MAG using hidden Markov models. The identified homologous genes of the marker genes are further aligned, concatenated, and then placed into the reference genome tree using pplacer for taxonomic inference and quality checking[59]. Another evaluation method for the assembled MAG is MetaQUAST, which aligns contig sequences of MAG to a close reference genome[60]. This program is able to detect potential taxonomic position of MAG by BLASTN searches against 16S rRNA sequences from the SILVA database[61,62]. Then it automatically downloads close reference genomes from the on-line NCBI database and aligns them against MAG for evaluation.

Different from the taxonomic assignment based on 16S rRNA sequencing, metagenome sequencing and assembly contain much more information than 16S rRNA sequences. Data mining strategies to obtain taxonomic information from large-scale metagenome assembly need to be considered and designed. As discussed above, both CheckM and MetaQUAST provide lineage hints for taxonomic assignment of MAGs[58,60]. Additionally, PhyloFlash maps sequencing reads to small-subunit rRNA (SSU rRNA) database for taxonomic assignment and can be performed before the metagenomes are assembled[63]. FOCUS uses non-negative least squares algorithm to compare k-mers between references genomes and MAGs, and determine taxonomic position for contigs binned in MAGs[64].

PREDICTION OF MICROBE-HOST INTERACTIONS

Gut microbes living in intestine mucosal, including commensals and pathogens, regulate homeostasis of host immunity[65]. Their activities are able to alter host signaling and immunity by interacting with the host proteins. Deciphering how microbe and host interact *via* protein-protein interactions and through which microbial and host proteins they work are important to development of novel strategies for prevention of CRC. Since wet-lab experiments are time-consuming and laborious, experimentally determining the microbe-host interactions is still challenging. On the other hand, genome-wide computational methods can efficiently provide hints to enhance our understanding of this challenging task[66-71]. One category of these computational methods are AI based methods for determining protein-protein interactions (PPI) between microbes and host[69,70]. Currently, AI based methods for PPI predictions are still new and only a few of them have been developed. Most of them are supervised methods, which utilizes well-recognized datasets as standards to train AI models and determine parameters. These training datasets are either collected from high-throughput experiments or obtained from literatures by text mining. Supervised PPI methods utilize various AI models such as logistic regression, random forests, support vector machine, artificial neural networks, and K-nearest neighbors [72-76]. However, these AI-based PPI methods are designed for the PPI relationship between specific pathogen and human such as human-*Bacillus anthracis*, human-*Yersinia pestis* and human-*Fusobacterium nucleatum*[67,77-79]. Because high abundances of *F. nucleatum* are associated with CRC patients and especially associated with specific CRC stages, *F. nucleatum* is proposed for its causal role in CRC development. Computational scanning of *F. nucleatum* genome and human proteins identified FusoSecretome proteins and their targets in the host network[67]. PPI-coupled network analysis identified that *F. nucleatum* perturbed host cellular pathways including immune and infection response, homeostasis, cytoskeleton organization, and gene expression regulation[67]. However, AI-based PPI studies for human-microbiome interactions still need more efforts due to the complex mixed-population of species within gut microbiome.

CONCLUSION

Rapid development of high-throughput sequencing and high-throughput screening experiments generate large-scale datasets and largely improve our understanding of functional roles of gut microbiomes in CRC evolution. Using AI-based analyses, potential pathogenic species from gut microbiome have been identified to play critical roles in driving CRC. However, there are still limitations in current methods and challenges remain for them to be improved. These include but not limited to the questions as follows. How to accurately identify bacterial species/strains that reside in gut mucosal? How to use metagenomics sequencing data to assemble complete or nearly complete MAGs for bacterial single species? How to build AI models to interpret human-microbiome interactions under different environmental conditions? And many more challenges remain to be solved. I believe that continuous improvement of AI technology in CRC diagnosis as well as many more diseases will facilitate answering the above questions and help develop clinical treatment and prevention of CRC in advance.

REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767 [PMID: 2188735 DOI: 10.1016/0092-8674(90)90186-i]

3 **Smit WL**, Spaan CN, Johannes de Boer R, Ramesh P, Martins Garcia T, Meijer BJ, Vermeulen JLM, Lezzerini M, MacInnes AW, Koster J, Medema JP, van den Brink GR, Muncan V, Heijmans J. Driver mutations of the adenoma-carcinoma sequence govern the intestinal epithelial global translational capacity. *Proc Natl Acad Sci U S A* 2020; **117**: 25560-25570 [PMID: 32989144 DOI: 10.1073/pnas.1912772117]

4 **Morley AA**, Turner DR. The contribution of exogenous and endogenous mutagens to *in vivo* mutations. *Mutat Res* 1999; **428**: 11-15 [PMID: 10517973 DOI: 10.1016/s1383-5742(99)00026-5]

5 **Stratton MR**, Campbell PJ, Futreal PA. The cancer genome. *Nature* 2009; **458**: 719-724 [PMID: 19360079 DOI: 10.1038/nature07943]

6 **Esteller M**. Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat Rev Genet* 2007; **8**: 286-298 [PMID: 17339880 DOI: 10.1038/nrg2005]

7 **Tjalsma H**, Boleij A, Marchesi JR, Dutilh BE. A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. *Nat Rev Microbiol* 2012; **10**: 575-582 [PMID: 22728587 DOI: 10.1038/nrmicro2819]

8 **Song M**, Chan AT. Environmental Factors, Gut Microbiota, and Colorectal Cancer Prevention. *Clin Gastroenterol Hepatol* 2019; **17**: 275-289 [PMID: 30031175 DOI: 10.1016/j.cgh.2018.07.012]

9 **Zhang S**, Cai S, Ma Y. Association between *Fusobacterium nucleatum* and colorectal cancer: Progress and future directions. *J Cancer* 2018; **9**: 1652-1659 [PMID: 29760804 DOI: 10.7150/jca.24048]

10 **Long X**, Wong CC, Tong L, Chu ESH, Ho Szeto C, Go MYY, Coker OO, Chan AWH, Chan FKL, Sung JJY, Yu J. Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity. *Nat Microbiol* 2019; **4**: 2319-2330 [PMID: 31501538 DOI: 10.1038/s41564-019-0541-3]

11 **Rhee KJ**, Wu S, Wu X, Huso DL, Karim B, Franco AA, Rabizadeh S, Golub JE, Mathews LE, Shin J, Sartor RB, Golenbock D, Hamad AR, Gan CM, Housseau F, Sears CL. Induction of persistent colitis by a human commensal, enterotoxigenic Bacteroides fragilis, in wild-type C57BL/6 mice. *Infect Immun* 2009; **77**: 1708-1718 [PMID: 19188353 DOI: 10.1128/IAI.00814-08]

12 **Wang Y**, Wan X, Wu X, Zhang C, Liu J, Hou S. Eubacterium rectale contributes to colorectal cancer initiation *via* promoting colitis. *Gut Pathog* 2021; **13**: 2 [PMID: 33436075 DOI: 10.1186/s13099-020-00396-z]

13 **Wang Y**, Zhang C, Hou S, Wu X, Liu J, Wan X. Analyses of Potential Driver and Passenger Bacteria in Human Colorectal Cancer. *Cancer Manag Res* 2020; **12**: 11553-11561 [PMID: 33209059 DOI: 10.2147/CMAR.S275316]

14 **Nakatsu G**, Li X, Zhou H, Sheng J, Wong SH, Wu WK, Ng SC, Tsoi H, Dong Y, Zhang N, He Y, Kang Q, Cao L, Wang K, Zhang J, Liang Q, Yu J, Sung JJ. Gut mucosal microbiome across stages of colorectal carcinogenesis. *Nat Commun* 2015; **6**: 8727 [PMID: 26515465 DOI: 10.1038/ncomms9727]

15 **Dadkhah E**, Sikaroodi M, Korman L, Hardi R, Baybick J, Hanzel D, Kuehn G, Kuehn T, Gillevet PM. Gut microbiome identifies risk for colorectal polyps. *BMJ Open Gastroenterol* 2019; **6**: e000297 [PMID: 31275588 DOI: 10.1136/bmjgast-2019-000297]

16 **Saito K**, Koido S, Odamaki T, Kajihara M, Kato K, Horiuchi S, Adachi S, Arakawa H, Yoshida S, Akasu T, Ito Z, Uchiyama K, Saruta M, Xiao JZ, Sato N, Ohkusa T. Metagenomic analyses of the gut microbiota associated with colorectal adenoma. *PLoS One* 2019; **14**: e0212406 [PMID: 30794590 DOI: 10.1371/journal.pone.0212406]

17 **Zhang M**, Lv Y, Hou S, Liu Y, Wang Y, Wan X. Differential Mucosal Microbiome Profiles across Stages of Human Colorectal Cancer. *Life (Basel)* 2021; **11** [PMID: 34440574 DOI: 10.3390/Life11080831]

18 **Dai Z**, Coker OO, Nakatsu G, Wu WKK, Zhao L, Chen Z, Chan FKL, Kristiansen K, Sung JJY, Wong SH, Yu J. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. *Microbiome* 2018; **6**: 70 [PMID: 29642940 DOI: 10.1186/s40168-018-0451-2]

19 **Chen F**, Dai X, Zhou CC, Li KX, Zhang YJ, Lou XY, Zhu YM, Sun YL, Peng BX, Cui W. Integrated analysis of the faecal metagenome and serum metabolome reveals the role of gut microbiome-associated metabolites in the detection of colorectal cancer and adenoma. *Gut* 2021 [PMID: 34462336 DOI: 10.1136/gutjnl-2020-323476]

20 **Mizutani S**, Yamada T, Yachida S. Significance of the gut microbiome in multistep colorectal carcinogenesis. *Cancer Sci* 2020; **111**: 766-773 [PMID: 31910311 DOI: 10.1111/cas.14298]

21 **Pleguezuelos-Manzano C**, Puschhof J, Rosendahl Huber A, van Hoeck A, Wood HM, Nomburg J, Gurjao C, Manders F, Dalmasso G, Stege PB, Paganelli FL, Geurts MH, Beumer J, Mizutani T, Miao Y, van der Linden R, van der Elst S; Genomics England Research Consortium, Garcia KC, Top J, Willems RJL, Giannakis M, Bonnet R, Quirke P, Meyerson M, Cuppen E, van Boxtel R, Clevers H. Mutational signature in colorectal cancer caused by genotoxic pks$^+$ E. coli. *Nature* 2020; **580**: 269-

273 [PMID: 32106218 DOI: 10.1038/s41586-020-2080-8]
22 **Sharma A**, Rani R. A systematic review of applications of machine learning in cancer prediction and diagnosis. *Arch Comput Methods Eng* 2021 [DOI: 10.1007/s11831-021-09556-z]
23 **Kourou K**, Exarchos TP, Exarchos KP, Karamouzis MV, Fotiadis DI. Machine learning applications in cancer prognosis and prediction. *Comput Struct Biotechnol J* 2015; **13**: 8-17 [PMID: 25750696 DOI: 10.1016/j.csbj.2014.11.005]
24 **Choi RY**, Coyner AS, Kalpathy-Cramer J, Chiang MF, Campbell JP. Introduction to Machine Learning, Neural Networks, and Deep Learning. *Transl Vis Sci Technol* 2020; **9**: 14 [PMID: 32704420]
25 **Pallen MJ**, Loman NJ, Penn CW. High-throughput sequencing and clinical microbiology: progress, opportunities and challenges. *Curr Opin Microbiol* 2010; **13**: 625-631 [PMID: 20843733 DOI: 10.1016/j.mib.2010.08.003]
26 **Lightbody G**, Haberland V, Browne F, Taggart L, Zheng H, Parkes E, Blayney JK. Review of applications of high-throughput sequencing in personalized medicine: barriers and facilitators of future progress in research and clinical application. *Brief Bioinform* 2019; **20**: 1795-1811 [PMID: 30084865 DOI: 10.1093/bib/bby051]
27 **Li W**, Jaroszewski L, Godzik A. Clustering of highly homologous sequences to reduce the size of large protein databases. *Bioinformatics* 2001; **17**: 282-283 [PMID: 11294794 DOI: 10.1093/bioinformatics/17.3.282]
28 **Li W**, Godzik A. Cd-hit: a fast program for clustering and comparing large sets of protein or nucleotide sequences. *Bioinformatics* 2006; **22**: 1658-1659 [PMID: 16731699 DOI: 10.1093/bioinformatics/btl158]
29 **Edgar RC**. Search and clustering orders of magnitude faster than BLAST. *Bioinformatics* 2010; **26**: 2460-2461 [PMID: 20709691 DOI: 10.1093/bioinformatics/btq461]
30 **Schloss PD**, Westcott SL, Ryabin T, Hall JR, Hartmann M, Hollister EB, Lesniewski RA, Oakley BB, Parks DH, Robinson CJ, Sahl JW, Stres B, Thallinger GG, Van Horn DJ, Weber CF. Introducing mothur: open-source, platform-independent, community-supported software for describing and comparing microbial communities. *Appl Environ Microbiol* 2009; **75**: 7537-7541 [PMID: 19801464 DOI: 10.1128/AEM.01541-09]
31 **Wang Q**, Garrity GM, Tiedje JM, Cole JR. Naive Bayesian classifier for rapid assignment of rRNA sequences into the new bacterial taxonomy. *Appl Environ Microbiol* 2007; **73**: 5261-5267 [PMID: 17586664 DOI: 10.1128/AEM.00062-07]
32 **Koparde VN**, Adkins RS, Fettweis JM, Serrano MG, Buck GA, Reimers MA, Sheth NU. BOTUX: bayesian-like operational taxonomic unit examiner. *Int J Comput Biol Drug Des* 2014; **7**: 130-145 [PMID: 24878725 DOI: 10.1504/IJCBDD.2014.061652]
33 **Gwak HJ**, Rho M. Data-Driven Modeling for Species-Level Taxonomic Assignment From 16S rRNA: Application to Human Microbiomes. *Front Microbiol* 2020; **11**: 570825 [PMID: 33262743 DOI: 10.3389/fmicb.2020.570825]
34 **Saitou N**, Nei M. The neighbor-joining method: a new method for reconstructing phylogenetic trees. *Mol Biol Evol* 1987; **4**: 406-425 [PMID: 3447015 DOI: 10.1093/oxfordjournals.molbev.a040454]
35 **Mailund T**, Brodal GS, Fagerberg R, Pedersen CN, Phillips D. Recrafting the neighbor-joining method. *BMC Bioinformatics* 2006; **7**: 29 [PMID: 16423304 DOI: 10.1186/1471-2105-7-29]
36 **Dhar A**, Minin VN. Maximum likelihood phylogenetic inference. *Ency Evol Bio* 2016; **2**: 499-506 [DOI: 10.1016/B978-0-12-800049-6.00207-9]
37 **Price MN**, Dehal PS, Arkin AP. FastTree 2--approximately maximum-likelihood trees for large alignments. *PLoS One* 2010; **5**: e9490 [PMID: 20224823 DOI: 10.1371/journal.pone.0009490]
38 **Sagulenko P**, Puller V, Neher RA. TreeTime: Maximum-likelihood phylodynamic analysis. *Virus Evol* 2018; **4**: vex042 [PMID: 29340210 DOI: 10.1093/ve/vex042]
39 **Thursby E**, Juge N. Introduction to the human gut microbiota. *Biochem J* 2017; **474**: 1823-1836 [PMID: 28512250 DOI: 10.1042/BCJ20160510]
40 **Swets DL**, Weng J. Using discriminant eigenfeatures for image retrieval. *IEEE Trans Pattern Anal Mach Intell* 1996; **18**: 831-836 [DOI: 10.1109/34.531802]
41 **Turk M**, Pentland A. Eigenfaces for recognition. *J Cogn Neurosci* 1991; **3**: 71-86 [PMID: 23964806 DOI: 10.1162/jocn.1991.3.1.71]
42 **Forster SC**, Kumar N, Anonye BO, Almeida A, Viciani E, Stares MD, Dunn M, Mkandawire TT, Zhu A, Shao Y, Pike LJ, Louie T, Browne HP, Mitchell AL, Neville BA, Finn RD, Lawley TD. A human gut bacterial genome and culture collection for improved metagenomic analyses. *Nat Biotechnol* 2019; **37**: 186-192 [PMID: 30718869 DOI: 10.1038/s41587-018-0009-7]
43 **Zerbino DR**, Birney E. Velvet: algorithms for de novo short read assembly using de Bruijn graphs. *Genome Res* 2008; **18**: 821-829 [PMID: 18349386 DOI: 10.1101/gr.074492.107]
44 **Bankevich A**, Nurk S, Antipov D, Gurevich AA, Dvorkin M, Kulikov AS, Lesin VM, Nikolenko SI, Pham S, Prjibelski AD, Pyshkin AV, Sirotkin AV, Vyahhi N, Tesler G, Alekseyev MA, Pevzner PA. SPAdes: a new genome assembly algorithm and its applications to single-cell sequencing. *J Comput Biol* 2012; **19**: 455-477 [PMID: 22506599 DOI: 10.1089/cmb.2012.0021]
45 **Luo R**, Liu B, Xie Y, Li Z, Huang W, Yuan J, He G, Chen Y, Pan Q, Liu Y, Tang J, Wu G, Zhang H, Shi Y, Yu C, Wang B, Lu Y, Han C, Cheung DW, Yiu SM, Peng S, Xiaoqian Z, Liu G, Liao X, Li Y, Yang H, Wang J, Lam TW. SOAPdenovo2: an empirically improved memory-efficient short-read de novo assembler. *Gigascience* 2012; **1**: 18 [PMID: 23587118 DOI: 10.1186/2047-217X-1-18]
46 **Kenny DJ**, Plichta DR, Shungin D, Koppel N, Hall AB, Fu B, Vasan RS, Shaw SY, Vlamakis H,

Balskus EP, Xavier RJ. Cholesterol Metabolism by Uncultured Human Gut Bacteria Influences Host Cholesterol Level. *Cell Host Microbe* 2020; **28**: 245-257.e6 [PMID: 32544460 DOI: 10.1016/j.chom.2020.05.013]

47 **Almeida A**, Mitchell AL, Boland M, Forster SC, Gloor GB, Tarkowska A, Lawley TD, Finn RD. A new genomic blueprint of the human gut microbiota. *Nature* 2019; **568**: 499-504 [PMID: 30745586 DOI: 10.1038/s41586-019-0965-1]

48 **Ayling M**, Clark MD, Leggett RM. New approaches for metagenome assembly with short reads. *Brief Bioinform* 2020; **21**: 584-594 [PMID: 30815668 DOI: 10.1093/bib/bbz020]

49 **Sedlar K**, Kupkova K, Provaznik I. Bioinformatics strategies for taxonomy independent binning and visualization of sequences in shotgun metagenomics. *Comput Struct Biotechnol J* 2017; **15**: 48-55 [PMID: 27980708 DOI: 10.1016/j.csbj.2016.11.005]

50 **Li D**, Liu CM, Luo R, Sadakane K, Lam TW. MEGAHIT: an ultra-fast single-node solution for large and complex metagenomics assembly *via* succinct de Bruijn graph. *Bioinformatics* 2015; **31**: 1674-1676 [PMID: 25609793 DOI: 10.1093/bioinformatics/btv033]

51 **Nurk S**, Meleshko D, Korobeynikov A, Pevzner PA. metaSPAdes: a new versatile metagenomic assembler. *Genome Res* 2017; **27**: 824-834 [PMID: 28298430 DOI: 10.1101/gr.213959.116]

52 **Kang DD**, Li F, Kirton E, Thomas A, Egan R, An H, Wang Z. MetaBAT 2: an adaptive binning algorithm for robust and efficient genome reconstruction from metagenome assemblies. *PeerJ* 2019; **7**: e7359 [PMID: 31388474 DOI: 10.7717/peerj.7359]

53 **Wu YW**, Simmons BA, Singer SW. MaxBin 2.0: an automated binning algorithm to recover genomes from multiple metagenomic datasets. *Bioinformatics* 2016; **32**: 605-607 [PMID: 26515820 DOI: 10.1093/bioinformatics/btv638]

54 **Alneberg J**, Bjarnason BS, de Bruijn I, Schirmer M, Quick J, Ijaz UZ, Lahti L, Loman NJ, Andersson AF, Quince C. Binning metagenomic contigs by coverage and composition. *Nat Methods* 2014; **11**: 1144-1146 [PMID: 25218180 DOI: 10.1038/nmeth.3103]

55 **Lin HH**, Liao YC. Accurate binning of metagenomic contigs *via* automated clustering sequences using information of genomic signatures and marker genes. *Sci Rep* 2016; **6**: 24175 [PMID: 27067514 DOI: 10.1038/srep24175]

56 **Graham ED**, Heidelberg JF, Tully BJ. BinSanity: unsupervised clustering of environmental microbial assemblies using coverage and affinity propagation. *PeerJ* 2017; **5**: e3035 [PMID: 28289564 DOI: 10.7717/peerj.3035]

57 **Uritskiy GV**, DiRuggiero J, Taylor J. MetaWRAP-a flexible pipeline for genome-resolved metagenomic data analysis. *Microbiome* 2018; **6**: 158 [PMID: 30219103 DOI: 10.1186/s40168-018-0541-1]

58 **Parks DH**, Imelfort M, Skennerton CT, Hugenholtz P, Tyson GW. CheckM: assessing the quality of microbial genomes recovered from isolates, single cells, and metagenomes. *Genome Res* 2015; **25**: 1043-1055 [PMID: 25977477 DOI: 10.1101/gr.186072.114]

59 **Matsen FA**, Kodner RB, Armbrust EV. pplacer: linear time maximum-likelihood and Bayesian phylogenetic placement of sequences onto a fixed reference tree. *BMC Bioinformatics* 2010; **11**: 538 [PMID: 21034504 DOI: 10.1186/1471-2105-11-538]

60 **Mikheenko A**, Saveliev V, Gurevich A. MetaQUAST: evaluation of metagenome assemblies. *Bioinformatics* 2016; **32**: 1088-1090 [PMID: 26614127 DOI: 10.1093/bioinformatics/btv697]

61 **Quast C**, Pruesse E, Yilmaz P, Gerken J, Schweer T, Yarza P, Peplies J, Glöckner FO. The SILVA ribosomal RNA gene database project: improved data processing and web-based tools. *Nucleic Acids Res* 2013; **41**: D590-D596 [PMID: 23193283 DOI: 10.1093/nar/gks1219]

62 **Yilmaz P**, Parfrey LW, Yarza P, Gerken J, Pruesse E, Quast C, Schweer T, Peplies J, Ludwig W, Glöckner FO. The SILVA and "All-species Living Tree Project (LTP)" taxonomic frameworks. *Nucleic Acids Res* 2014; **42**: D643-D648 [PMID: 24293649 DOI: 10.1093/nar/gkt1209]

63 **Gruber-Vodicka HR**, Seah BKB, Pruesse E. phyloFlash: Rapid Small-Subunit rRNA Profiling and Targeted Assembly from Metagenomes. *mSystems* 2020; **5** [PMID: 33109753 DOI: 10.1128/mSystems.00920-20]

64 **Silva GG**, Cuevas DA, Dutilh BE, Edwards RA. FOCUS: an alignment-free model to identify organisms in metagenomes using non-negative least squares. *PeerJ* 2014; **2**: e425 [PMID: 24949242 DOI: 10.7717/peerj.425]

65 **Pickard JM**, Zeng MY, Caruso R, Núñez G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. *Immunol Rev* 2017; **279**: 70-89 [PMID: 28856738 DOI: 10.1111/imr.12567]

66 **Zuñiga C**, Zaramela L, Zengler K. Elucidation of complexity and prediction of interactions in microbial communities. *Microb Biotechnol* 2017; **10**: 1500-1522 [PMID: 28925555 DOI: 10.1111/1751-7915.12855]

67 **Zanzoni A**, Spinelli L, Braham S, Brun C. Perturbed human sub-networks by Fusobacterium nucleatum candidate virulence proteins. *Microbiome* 2017; **5**: 89 [PMID: 28793925 DOI: 10.1186/s40168-017-0307-1]

68 **Magnúsdóttir S**, Heinken A, Kutt L, Ravcheev DA, Bauer E, Noronha A, Greenhalgh K, Jäger C, Baginska J, Wilmes P, Fleming RM, Thiele I. Generation of genome-scale metabolic reconstructions for 773 members of the human gut microbiota. *Nat Biotechnol* 2017; **35**: 81-89 [PMID: 27893703 DOI: 10.1038/nbt.3703]

69 **Lian X**, Yang S, Li H, Fu C, Zhang Z. Machine-Learning-Based Predictor of Human-Bacteria Protein-Protein Interactions by Incorporating Comprehensive Host-Network Properties. *J Proteome*

Res 2019; **18**: 2195-2205 [PMID: 30983371 DOI: 10.1021/acs.jproteome.9b00074]

70 **Guven-Maiorov E**, Hakouz A, Valjevac S, Keskin O, Tsai CJ, Gursoy A, Nussinov R. HMI-PRED: A Web Server for Structural Prediction of Host-Microbe Interactions Based on Interface Mimicry. *J Mol Biol* 2020; **432**: 3395-3403 [PMID: 32061934 DOI: 10.1016/j.jmb.2020.01.025]

71 **Jansma J**, El Aidy S. Understanding the host-microbe interactions using metabolic modeling. *Microbiome* 2021; **9**: 16 [PMID: 33472685 DOI: 10.1186/s40168-020-00955-1]

72 **Prasasty VD**, Hutagalung RA, Gunadi R, Sofia DY, Rosmalena R, Yazid F, Sinaga E. Prediction of human-Streptococcus pneumoniae protein-protein interactions using logistic regression. *Comput Biol Chem* 2021; **92**: 107492 [PMID: 33964803 DOI: 10.1016/j.compbiolchem.2021.107492]

73 **Wei ZS**, Yang JY, Shen HB, Yu DJ. A Cascade Random Forests Algorithm for Predicting Protein-Protein Interaction Sites. *IEEE Trans Nanobioscience* 2015; **14**: 746-760 [PMID: 26441427 DOI: 10.1109/TNB.2015.2475359]

74 **Chakraborty A**, Mitra S, De D, Pal AJ, Ghaemi F, Ahmadian A, Ferrara M. Determining Protein–Protein Interaction Using Support Vector Machine: A Review. *IEEE Access* 2021; **9**: 12473-12490 [DOI: 10.1109/ACCESS.2021.3051006]

75 **Tsuchiya Y**, Tomii K. Neural networks for protein structure and function prediction and dynamic analysis. *Biophys Rev* 2020; **12**: 569-573 [PMID: 32166610 DOI: 10.1007/s12551-020-00685-6]

76 **Suratanee A**, Plaimas K. Reverse Nearest Neighbor Search on a Protein-Protein Interaction Network to Infer Protein-Disease Associations. *Bioinform Biol Insights* 2017; **11**: 1177932217720405 [PMID: 28757797 DOI: 10.1177/1177932217720405]

77 **Ahmed I**, Witbooi P, Christoffels A. Prediction of human-Bacillus anthracis protein-protein interactions using multi-layer neural network. *Bioinformatics* 2018; **34**: 4159-4164 [PMID: 29945178 DOI: 10.1093/bioinformatics/bty504]

78 **Dyer MD**, Neff C, Dufford M, Rivera CG, Shattuck D, Bassaganya-Riera J, Murali TM, Sobral BW. The human-bacterial pathogen protein interaction networks of Bacillus anthracis, Francisella tularensis, and Yersinia pestis. *PLoS One* 2010; **5**: e12089 [PMID: 20711500 DOI: 10.1371/journal.pone.0012089]

79 **Yang H**, Ke Y, Wang J, Tan Y, Myeni SK, Li D, Shi Q, Yan Y, Chen H, Guo Z, Yuan Y, Yang X, Yang R, Du Z. Insight into bacterial virulence mechanisms against host immune response *via* the Yersinia pestis-human protein-protein interaction network. *Infect Immun* 2011; **79**: 4413-4424 [PMID: 21911467 DOI: 10.1128/IAI.05622-11]

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AIMS AND SCOPE

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

AIC mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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MINIREVIEWS

Artificial intelligence in colorectal cancer management

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Abstract

Artificial intelligence (AI) is a new branch of computer science involving many disciplines and technologies. Since its application in the medical field, it has been constantly studied and developed. AI includes machine learning and neural networks to create new technologies or to improve existing ones. Various AI supporting systems are available for a personalized and novel strategy for the management of colorectal cancer (CRC). This mini-review aims to summarize the progress of research and possible clinical applications of AI in the investigation, early diagnosis, treatment, and management of CRC, to offer elements of knowledge as a starting point for new studies and future applications.

Key Words: Artificial intelligence; Oncology; Colorectal cancer; Digestive surgery; Computer-assisted diagnosis

Core Tip: Many authors have summarized artificial intelligence applications in the field of cancer. This mini-review intends to open a window on the attempts being made on the application of artificial intelligence in the scientific and clinical research of colorectal cancer by summarizing the most evident results. Our aim is not to draw definitive conclusions but to stimulate the interest of researchers in the application of these new technologies, which seem to be able to offer valuable help in the near future.

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INTRODUCTION

Colorectal cancer (CRC) is a growing disease around the world. It represents the third leading cause of cancer in males, the second in female patients, and fourth in the world for the cause of cancer death[1,2]. In 2015, 777987 new cases and 352589 deaths due to CRC were estimated in developed countries[3,4]. According to the Surveillance, Epidemiology, and End results program, the 5-year relative survival rate is between 63% and 67% for colon and rectal cancer, respectively[5]. Although important progress has been made in terms of understanding and treating CRC, morbidity and mortality rates based on recurrence and metastasis in therapy remain high[6-8]. The estimate of cases diagnosed at an advanced stage in asymptomatic patients is about 60%-70%[9-11]. High incidence, high mortality, and often poor prognosis make this disease not only a major health problem but also a social and economic one. For some years, early diagnosis and treatment of CRC patients have been the main clinical commitment. The research on the application of artificial intelligence (AI) in the treatment of CRC is still in its initial phase; however, with its continuous development and its major applications in the field of medicine, it is now taking off, also in the management of malignant colorectal disease. AI refers to a type of intelligence exhibited by machines that are able to perceive their environment and act autonomously in achieving their goals[12]. AI technology has been used extensively in medicine, business, and relationship life. In health science, AI is used especially for the diagnosis, treatment, and prognosis of diseases. In medicine, AI is divided into two sectors: Virtual and physical. The former includes imaging techniques, clinical assistant diagnosis, treatment, research, and drug development. The latter includes surgical and nursing robotic automation[13] (Figure 1). The continuous expansion and application of AI in the medical field are increasing its applicative prospects for the diagnosis and treatment of tumors. Recent studies have shown that AI can play an important role in the diagnosis and treatment of CRC patients, and it can not only improve the efficiency of screening, but can also improve the 5-year survival rate of CRC patients after treatment. This mini-review covers a period of 20 years with particular attention to the last decade, and intends to open a window on the attempts being made on the application of AI in the scientific and clinical research of the CRC by summarizing the most evident results. Our aim is not to draw definitive conclusions but to stimulate the interest of researchers in the application of these new technologies, which seem to be able to offer valuable help in the near future.

EPIDEMIOLOGY

AI is an operative modality that can improve the collection of medical data for epidemiology purposes. Its predictive value is one of the most practical applications of this technology[14], already verified in areas such as public health and safety; on the other hand, it has not shown the same results when applied to the management of malignant diseases such as cancer. In 2016, CRC was responsible for approximately 8.2% of all cancer deaths in the United States, ranking as the third leading cause of cancer deaths regardless of gender[15]. In fact, we wonder how AI can positively influence the epidemiology of CRC. The first steps in epidemiology concern general measures such as the interpretation of research and data. There are often some difficulties regarding access to data and their categorization, and these methods are still under development[16-19]. Regarding CRC, an aspect of AI called GeoAI is a tool that can potentially help health care, and it is a system that collects information and data from a specific geographic area (food, type of soil, health system available, *etc*.) allowing them to be retrieved in a more specific and detailed form on the basis of what is desired[20]. Hungary and South Korea are the countries with the highest incidence of CRC[21], and CRC, like other gastrointestinal cancers, involves a complex and multifactorial process that is also influenced by geographic location, genetic predisposition, nutrition, lifestyles, and specific habits[22]. Due to this multifactoriality, systems such as GeoAI could have a great utility in defining more precisely the epidemiology of CRC by providing increasingly specific data sets in order to improve knowledge even at a local level. The hope is that specific areas with a high incidence of CRC will benefit from this type of information collection. Another application of AI is digital epidemiology which deals with the collection of information such as the collection of epidemiological data from social media and digital devices which are then quantified by AI[23]. Digital epidemiology has the great advantage of collecting huge amounts of data that have not been previously planned, but are instead

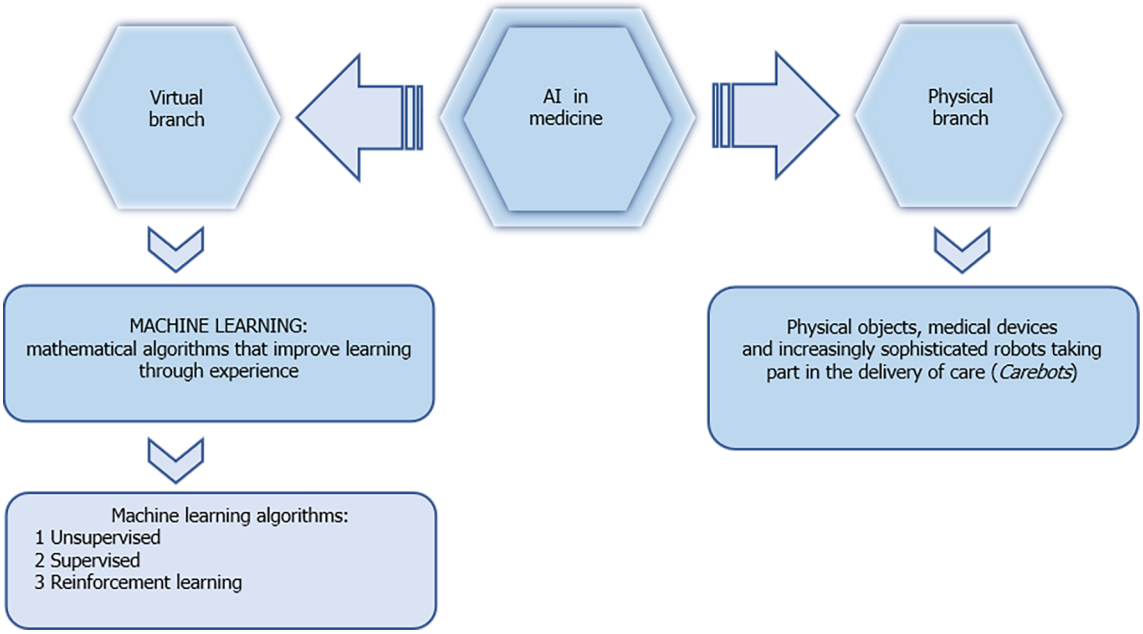

Figure 1 Artificial intelligence in medicine.

voluntarily provided by people online[24]. This provides a huge pool of information that was not previously available to physicians and can aid in the early diagnosis of disease and health surveillance of the general public[25]. The disadvantage is the risk of violation of the patient's privacy which can bring out issues on information security and confidentiality[19,26]. Although the collection of information sets is considered tedious and not very useful, an advantageous tool for collecting and ordering them in order to produce something relevant is the data mining[27] that uses AI to collect much information, related or unrelated, trying to create a useful order to propose models and find facts[28]. This process involves the creation of databases, with selection and integration of data, storage and extraction of the most relevant ones, and proposal of models with subsequent evaluation and knowledge deriving from this information[28]. Therefore, medical data on CRC can come from different sources (social web, tertiary or research centers, *etc*.), but what is considered useful is the knowledge that they can bring and the use that can result from it. For CRC, data mining can represent a technological tool capable of implementing and promoting the discovery of relationships, new associations and other factors never even considered before which nevertheless may play a role in this multifactorial disease.

DIAGNOSIS

For many researchers, AI is seen as an approach that will help to better understand diseases and facilitate their management, and in this discourse it could not be excluded that slowly implemented ways can better diagnose cancer and treat patients with greater accuracy and precision[29]. Deep learning has attempted to examine how medical imaging can be improved and how to find cancer using imaging, and ranges from tools that enable a greater ability to scan and interpret images faster, high workflow, and better definition or improve image quality and its extraction with 3D technology[30-33]. Diagnosis is the integration of multi-source data analysis and clinical experience. Cancer manifests a wide variety of symptoms, rapid progression, drug susceptibility, and individual reactions, and for these reasons it is difficult to make an accurate diagnosis. AI has been shown to help clinicians in the qualitative diagnosis and staging of CRC[34].

Endoscopy is used to directly observe lesions in the intestinal wall, and endoscopists through images can assess whether the lesions are related to CRC. Lefere *et al*[35] in 2006 introduced the concept of virtual colonoscopy. This innovative examination is based on computed tomography colonography[36], in which the images are processed into three-dimensional cavity images. The images thus produce simulated optical colonoscopy with the aim of detecting CRCs and their adenomatoid

polypoid precursors, or other neoplastic lesions. The advent of AI has made colonoscopy a convenient and accurate examination for CRC screening. In 2016, Fernandez-Esparrach *et al*[37] designed a method that automatically detected colon polyps. Their work achieved a sensitivity of 70.4% and specificity of 72.4%, and consisted of inserting 31 types of information about polyps into a computerized learning system. In 2012, Takemura *et al*[38] used narrow band imaging (NBI) and support vector machine (SVM) technology to distinguish neoplastic polyps from non-neoplastic polyps, resulting in a detection accuracy of 97.8%. Urban *et al*[39] designed and trained a convolutional neural network (CNN) system to improve adenoma recognition rate for colonoscopy. They collected images from over 2000 colonoscopy results for machine learning. Their assistant system achieved an accuracy of 96.4%. Mori *et al*[40] mixed NBI with staining image technology to recognize images of small malignant polyps being screened in real time. The final pathological forecast that they obtained was 98.1%. Akbari *et al*[41] used polyp segmentation during colonoscopy to recognize tumors using a CNN. During the testing phase, they conducted effective post-processing of a probability graph extrapolated from their CNN, reaching a specificity of 74.8%, sensitivity of 99.3%, and accuracy of 97.7%. Renner[42] have structured a computer-assisted optical biopsy system. They uploaded 602 images to the deep learning system for each colorectal tract examined endoscopically. By processing the information contained in the images, they were able to distinguish the neoplastic polyps with a diagnostic accuracy and sensitivity of 78.0% and 92.3%, respectively. Other authors[43], according to available evidence, conclude that the incorporation of AI as an aid for detection of colorectal neoplasia results in a significant increase in the detection of colorectal neoplasia, and such effect is independent from main adenoma characteristics. EndoBRAIN is an AI-assisted endoscopic diagnosis system that analyzes cell nuclei, crypt structures, and microvessels, with the aim of identifying colonic neoplasms. In 2020, Kudo *et al*[44] performed a retrospective comparison between the diagnostic capabilities of the EndoBRAIN system and those of 30 endoscopists. During the analysis, EndoBRAIN showed a sensitivity of 96.9%, specificity of 94.3%, and accuracy of 96.0% in distinguishing neoplastic from non-neoplastic lesions. The endoscopists' values were lower. Blanes-Vidal *et al*[45] extended the use of AI for capsule endoscopy through the use of a CNN for the detection and localization of colon polyps. The results of their algorithm were excellent, reaching an accuracy of 96.4%, while the sensitivity and specificity were 97.1% and 93.3%, respectively. During colonoscopy, the mucosa of malignant colon tumors is characterized by irregular and discontinuous crypt structures, and help in diagnosis can be provided by computer-assisted diagnosis (CAD). In 2015, the Infocus-Breakpoint was designed, which is a method that can directly detect the length and area of a neoplasm by transforming it into a 2D colonoscopic image, with great precision[46]. CAD was used by Ştefănescu[47] for processing images from confocal laser endomicroscopy and training the model using a two-layered feed forward neural network for diagnosing malignant samples based on seven parameters tested. The diagnostic error obtained was 15.5%. NBI magnification (M-NBI) can be employed for detailed observations of microvascular structures. In this regard, Tamai *et al*[48] used M-NBI-based CAD to classify and list mucosal lesions in the colon, including hyperplastic polyps, adenoma/adenocarcinoma lesions, and deep submucosal lesions, with an accuracy of 83.9%, 82.6%, 53.1%, 95.6%, and 82.8%, respectively. The development of CRC is a process consisting of many steps, and the transformation from adenoma to carcinoma[49] can take a very long time. Therefore, the importance of early screening and detection of lesions to reduce the incidence of this disease is intuitive[50]. In this regard, Ito *et al*[51] developed an AI system applied to endoscopy for diagnosis, and this system was based on a CNN using machine learning images. The authors analyzed protruding, flat, and sunken lesions and found improvement for colon cancer detection. The sensitivity, specificity, and accuracy found for cT1b were 67.5%, 89.0%, and 81.2%, respectively. Subsequently, several CAD systems were developed to screen patients at risk for CRC prior to colonoscopy. Some authors have developed AI systems with the aim of analyzing patient information comprehensively to predict the onset of CRC. The variables selected were gender, age, and blood test data. In this case, the objective in addition to the scientific purpose represented an encouragement for patients with positive results in order to induce them to accept periodic checks[52]. In 2018, Xu *et al*[53] assembled a team that designed an early screening method for CRC based on plasma copy number variation. They sequenced entire genomes and then trained an SVM to make the diagnosis. The results obtained by this method were an 88.9% specificity and a sensitivity of 91.7%. Recently, Graham *et al*[54] proposed MILD-Net, a CNN composed of a completely convolutive network, and this system has reintroduced the original images at multiple points within their

network in order to reduce diagnostic uncertainty. Other authors such as Wan *et al*[55] designed an AI program with the intent of improving the sensitivity of the extraction of plasma cell-free DNA for CRC patients. For a weighted early (stage I/II) CRC cohort, they achieved an average sensitivity of 85%. Wang *et al*[56] has designed several artificial neural networks (ANN) models that are biologically inspired computer programs designed to simulate the way in which the human brain processes information. Using a vector quantization neural network, they structured four models for qualitative diagnosis, M0/M1 discrimination, carcinoembryonic antigen testing, and clinical staging. Shahbazy *et al*[57] have included some classification factors in his algorithm, concerning a case-control study, demonstrating greater accuracy in the early diagnosis of CRC. The 5-year disease-free survival rate was 84%. Tumor budding is considered a sign of cancer cell activity and the first step of tumor metastasis. In accordance with this concept, Liu[58] in 2021 established an automatic diagnostic platform for rectal cancer budding pathology by training a faster region-based CNN (F-R-CNN) on the pathological images of rectal cancer budding. He analyzed postoperative pathological section images of 236 patients with rectal cancer. The conclusions were that F-R-CNN deep neural network platform for the pathological diagnosis of rectal cancer tumor budding can help pathologists make more efficient and accurate pathological diagnoses. Gupta *et al*[59] proposed a study on over 4000 CRC patients, using machine learning algorithms to predict the stage of the tumor. They postulated that tumor budding may be an additional prognostic factor to the TNM staging system. To overcome the problem of the poor reliability of tumor budding, Weis *et al*[60] introduced a different automatic image processing tool to quantify it in immunohistochemistry sections. Detections of tumor buds in CRC patient samples were reliable. To increase the results of AI against CRC, histopathology and genetics may not be enough, in fact, as shown by a study by Borkowski *et al*[61] who compared different AI platforms to detect adenocarcinoma in the veteran population. They found significant difficulty, on the part of machine learning tools, in differentiating adenocarcinoma with KRAS mutation from those without KRAS mutation. These difficulties may suggest the need for a more unified approach. Environmental causes should not be underestimated in the formation of CRC cancer. However, the study of tumor suppressor genes and oncogenes such as *APC*, *KRAS*, and *MTHFR* occupy a no less important role[62]. This has led to a dramatic increase in the number of potential biomarkers and indicators that can be linked to cancer growth. Some success has been achieved through AI training to classify tumors based on histopathology alone. Some authors[63] have trained an algorithm to classify gastric and epithelial tumors into adenocarcinoma, adenoma, or non-neoplastic lesions. They compared a type of CNN that uses smaller tile sizes to RNN (recurrent neural network) to observe and then classify the images. The RNN was more accurate and no statistical difference was demonstrated. Ciompi *et al*[64] postulated that CNNs need better image quality and this could help AI approach. Late diagnosis of CRC can lead to other problems and we are nowhere near the solution, but AI could help in other ways for CRC diagnosis at a later stage. A study by Dimitriou *et al*[65] sought to increase the accuracy in prognosis for stage II cancers, ultimately arguing that more attention should be paid to traits such as textures, spatial relationships, and morphology, all of which can be better managed by machine learning. Another tool that could be useful in diagnosing CRC is represented by fuzzy systems[66], and these allow any number between 0 and 1 to exist. This scope can be applied to any form of pathology and can help identify aberrations or predict the likelihood of cancer based on predetermined parameters. In the case of colorectal polyps, fuzzy parameters can be easily applied to match various characteristics as a stock of polyps in pedunculate or mucous lesions, if the indentations on hyperplastic polyps will become advanced lesions and specific sizes or forms, and to categorize low-risk injuries or if an adenomatous polyp is at risk of canceration.

GENETIC TESTING

AI can also be important in genetic testing for CRC. Hu *et al*[67], based on gene expression, compared the accuracies of three different neural networks for cancer classification. On a sample of 53 patients, they found that the most accurate classification was obtained with the S-Kohonen neural network. In 2017, Xu *et al*[68] structured an SVM system to identify differentially expressed genes with the purpose of distinguishing patients with high risk and predicting prognoses. Fifteen genetic markers were identified as predictors of recurrence risk and prognosis for colon cancer

patients. Zhang *et al*[69] developed a counter-propagation ANN for the detection of the *BRAF* gene mutation in CRC using near-infrared testing. Their model achieved a diagnostic sensitivity of 100%, specificity of 87.5%, and accuracy of 93.8%, and it can distinguish the *BRAF V600E* mutation from the wild type.

Methylated DNA has been widely used in AI diagnosis as a biomarker for early CRC. Coppede *et al*[70] in 2015 structured an ANN to explore the association between CRC-related genes and environmental factors. They concluded that ANNs revealed the complexity of the interconnections among factors linked to DNA methylation in CRC, and also observed an intricate network of interconnections between dietary and lifestyle factors and the methylation profiles of the studied genes. Kel *et al*[71] developed an analytical method to diagnose early CRC by extracting human methylated cytosine and guanine separated by a phosphate (CpG) from blood and feces. This study involved 300 CRC patients and identified six potential epigenetic biomarkers of DNA methylation that may lead to rapid tumor development.

MANAGEMENT AND TREATMENT

In 2019 Ferrari *et al*[72] reported that AI, based on the analysis of the texture of MR images, would be able to settle the complete therapeutic response of rectal cancer previously subjected to neoadjuvant chemotherapy. Their results have been encouraging. Indeed, the proposed AI model allows the distinction between complete response to therapy and non-response in neoadjuvant treatment of rectal cancer. The role of AI in drug metabolism in the treatment of CRC is not to be neglected, and it can allow a better understanding of the transformation and metabolism that drugs induce towards cancer progression. Tools that assist AI provide reliable information on the metabolism of these drugs in the treatment of CRC, leading to a better understanding of their biological behavior and specific metabolic pathways[73]. The predictive power of AI in CRC through the use of the ANN algorithm is increasingly appreciated. Indeed, the ANN uses non-linear models with particular flexibility regarding medical research and clinical practice[74,75]. An advantage could be to optimize the process through flexible models with good value for money, and for large data collections. The ANN has proven to be an accurate and reliable tool for clinical decision making. Lastly, academic dissemination of knowledge is facilitated by these models[74-78]. According to a systematic review of 27 studies that used ANNs as diagnostic or prognostic tools, 21 of these showed health care benefits, while the others showed similar results to models already in use[74]. In this regard, other authors reported that the ANN applied to the prediction of distant metastasis of CRC showed a better outcome[79]. Traditionally, the treatment of CRC is multimodal, integrating surgery, chemotherapy, radiotherapy, and immunotherapy, and aims to offer together a complete and more effective cure. AI can be an extra help for patients to choose the treatment methods that are appropriate for them and improve the healing effects of the protocols in use by designing more individualized and precise therapies.

PERSONALIZATION AND DIVERSIFICATION OF THERAPEUTIC MANAGEMENT

Cancer research is moving towards the personalization of cancer treatments. Healthcare is rapidly moving toward precision or personalized medicine. Machine learning models have the potential to contribute to individual-based cancer care and transform the future of medicine[80]. The Watson for Oncology system was developed at Memorial Sloan Kettering Cancer Center. This AI-based system, by automatically extracting medical information from medical records and translating it into a practical language for learning, improves personalized and precision medical treatment for cancer therapy. This tool has been evaluated by various authors. Kim in 2019[81] analyzed the concordance rate between different chemotherapy regimens in the treatment of CRC, and the data were compared between those determined by a multidisciplinary team and those suggested by the recommendations of the Watson for Oncology: In 61 CRC samples, the rate of initial agreement was 46.4%, but after inclusion of other recommendations, it increased to 88.4%. It would appear that this system can be improved through continuous adjustments. Miyano[82] has also used the Watson for Oncology system for the genetic sequencing of cancer patients, and the results obtained in a very rapid time have produced a reduction in waiting times,

which is very useful when the topic under discussion is cancer. Akturk and Erci[83] experimented with this model applied to human care, finding more individualized and caring nursing services with patient satisfaction. With regard to these pathologies, medicine is becoming more and more personalized and also for the drugs used. In this sense, Keshava *et al*[84] proposed a method that can identify subpopulations that have different reactions towards inhibitors of the same target and can help to understand the mechanisms of resistance. With a system in continuous information enrichment, new subpopulations of cancer could be identified, and old and new genetic biomarkers were analyzed in order to find more effective combinations of drugs. Still with regard to the application of AI on targeted drugs, Ding *et al*[85] created a system for screening molecular markers at the system biology level by integrating transcriptomics and proteomics data. The identified markers were integrated to develop targeted drugs useful for the clinical treatment of CRC. Nowak-Sliwinska *et al*[86] proposed a study using existing anticancer drugs to treat new indications. They combined specific phenotypic studies with mechanistic studies to create AI models capable of predicting disease-drug pairs. Finally, clinical management also cannot be neglected. Horta *et al*[87] in 2018 collected information from CRC surgical patients, and then instructed a model to support decisions regarding selection of patients who should be offered co-management services.

LIMITS AND FUTURE PERSPECTIVES

With regard to new technologies such as AI, there is often a doubtful attitude, and the health staff bases their work and commitment on certain and verified information. However, in the era of big data, it will be necessary to address these issues and certainly deepen them in order to understand how reliable they are and the help that these methods can give us. The next step should be the creation of medical ethics guidelines, in order to regulate the scope of the use of these new technologies. It is necessary to understand the data in order to draw firm conclusions. The limit of all this technology is the insufficiency of aggregate and understandable data that allow us to draw advantageous conclusions. Taking the studies on the subject of CT imaging and AI as an example, the input data can be manifold, and this can represent a problem when definitive answers must be given for the diagnosis and treatment of the general population. The data optimization that the new technologies offer us requires and will require an investment of more and more time and money, but this will allow us to build systems that will allow better data collection and that will allow better and more accurate decision-making processes. The more institutions that start accumulating data, the greater their quantity and quality. The creation of public databases for information such as symptomatology, different imaging modalities, or geographic distribution can be a great strength that could benefit researchers by having access to more and more information. Free access to this data represents another obstacle that should not be underestimated, and underdeveloped and poor countries may not be able to have access to this technology. The further on we will go with the experimentation and application of AI, the more costs will decrease and the greater will be the benefits that can be felt by everyone and not only by those in certain geographical areas. It is critical for the global health community that these countries have access to technology to better treat and address diseases in their area and improve the quality of life in their local communities.

CONCLUSION

All new technologies can represent the beginning of a new era and their applications in daily use take time to be slowly incorporated. AI is certainly a promise of a new scientific season, but it remains at an early stage for its true application. Several researches on their use are slowly moving in a good direction. To date, it is clear that the methods of information gathering, diagnosis, and treatment of CRC will greatly improve through the use of deep learning tools. While the methods of obtaining medical information may be controversial, we can say with certainty that early detection of CRC will gain a great deal when appropriate methods for data collection are found. Ultimately, AI shows great promise in clinical and therapeutic management for CRC, and this could indicate better and more personalized treatments for patients with this disease.

REFERENCES

1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

2 **Maida M**, Morreale G, Sinagra E, Ianiro G, Margherita V, Cirrone Cipolla A, Camilleri S. Quality measures improving endoscopic screening of colorectal cancer: a review of the literature. *Expert Rev Anticancer Ther* 2019; **19**: 223-235 [PMID: 30614284 DOI: 10.1080/14737140.2019.1565999]

3 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

4 **He X**, Li S, Yu B, Kuang G, Wu Y, Zhang M, He Y, Ou C, Cao P. Up-regulation of *LINC00467* promotes the tumourigenesis in colorectal cancer. *J Cancer* 2019; **10**: 6405-6413 [PMID: 31772673 DOI: 10.7150/jca.32216]

5 **American Cancer Society**. Survival Rates for Colorectal Cancer. [cited 15 March 2021]. Available from: https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html

6 **Siegel RL**, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A. Colorectal cancer statistics, 2017. *CA Cancer J Clin* 2017; **67**: 177-193 [PMID: 28248415 DOI: 10.3322/caac.21395]

7 **Wang Y**, Nie H, He X, Liao Z, Zhou Y, Zhou J, Ou C. The emerging role of super enhancer-derived noncoding RNAs in human cancer. *Theranostics* 2020; **10**: 11049-11062 [PMID: 33042269 DOI: 10.7150/thno.49168]

8 **Ou C**, Sun Z, Li S, Li G, Li X, Ma J. Dual roles of yes-associated protein (YAP) in colorectal cancer. *Oncotarget* 2017; **8**: 75727-75741 [PMID: 29088905 DOI: 10.18632/oncotarget.20155]

9 **Mandel JS**, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365-1371 [PMID: 8474513 DOI: 10.1056/NEJM199305133281901]

10 **Maida M**, Macaluso FS, Ianiro G, Mangiola F, Sinagra E, Hold G, Maida C, Cammarota G, Gasbarrini A, Scarpulla G. Screening of colorectal cancer: present and future. *Expert Rev Anticancer Ther* 2017; **17**: 1131-1146 [PMID: 29022408 DOI: 10.1080/14737140.2017.1392243]

11 **Sinagra E**, Badalamenti M, Maida M, Spadaccini M, Maselli R, Rossi F, Conoscenti G, Raimondo D, Pallio S, Repici A, Anderloni A. Use of artificial intelligence in improving adenoma detection rate during colonoscopy: Might both endoscopists and pathologists be further helped. *World J Gastroenterol* 2020; **26**: 5911-5918 [PMID: 33132644 DOI: 10.3748/wjg.v26.i39.5911]

12 **Francolini G**, Desideri I, Stocchi G, Salvestrini V, Ciccone LP, Garlatti P, Loi M, Livi L. Artificial Intelligence in radiotherapy: state of the art and future directions. *Med Oncol* 2020; **37**: 50 [PMID: 32323066 DOI: 10.1007/s12032-020-01374-w]

13 **Hamet P**, Tremblay J. Artificial intelligence in medicine. *Metabolism* 2017; **69S**: S36-S40 [PMID: 28126242 DOI: 10.1016/j.metabol.2017.01.011]

14 **Chen JH**, Asch SM. Machine Learning and Prediction in Medicine - Beyond the Peak of Inflated Expectations. *N Engl J Med* 2017; **376**: 2507-2509 [PMID: 28657867 DOI: 10.1056/NEJMp1702071]

15 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**: 7-30 [PMID: 26742998 DOI: 10.3322/caac.21332]

16 **Thiébaut R**, Cossin S; Section Editors for the IMIA Yearbook Section on Public Health and Epidemiology Informatics. Artificial Intelligence for Surveillance in Public Health. *Yearb Med Inform* 2019; **28**: 232-234 [PMID: 31419837 DOI: 10.1055/s-0039-1677939]

17 **Thiébaut R**, Thiessard F; Section Editors for the IMIA Yearbook Section on Public Health and Epidemiology Informatics. Artificial Intelligence in Public Health and Epidemiology. *Yearb Med Inform* 2018; **27**: 207-210 [PMID: 30157525 DOI: 10.1055/s-0038-1667082]

18 **Rodríguez-González A**, Zanin M, Menasalvas-Ruiz E. Public Health and Epidemiology Informatics: Can Artificial Intelligence Help Future Global Challenges? *Yearb Med Inform* 2019; **28**: 224-231 [PMID: 31419836 DOI: 10.1055/s-0039-1677910]

19 **Denecke K**. An ethical assessment model for digital disease detection technologies. *Life Sci Soc Policy* 2017; **13**: 16 [PMID: 28929347 DOI: 10.1186/s40504-017-0062-x]

20 **Janowicz K**, Gao S, McKenzie G, Hu Y, Bhaduri B. GeoAI: Spatially Explicit Artificial Intelligence Techniques for Geographic Knowledge Discovery and Beyond. *Int J Geogr Inf Sci* 2020; 625-636 [DOI: 10.1080/13658816.2019.1684500]

21 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

22 **Kuipers EJ**, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, van de Velde CJ, Watanabe T. Colorectal cancer. *Nat Rev Dis Primers* 2015; **1**: 15065 [PMID: 27189416 DOI: 10.1038/nrdp.2015.65]

23 **Velasco E**. Disease detection, epidemiology and outbreak response: the digital future of public health practice. *Life Sci Soc Policy* 2018; **14**: 7 [PMID: 29607463 DOI: 10.1186/s40504-018-0071-4]

24 **Tarkoma S**, Alghnam S, Howell MD. Fighting pandemics with digital epidemiology. *EClinicalMedicine* 2020; **26**: 100512 [PMID: 32864592 DOI: 10.1016/j.eclinm.2020.100512]

25 **Eckmanns T**, Füller H, Roberts SL. Digital epidemiology and global health security; an

interdisciplinary conversation. *Life Sci Soc Policy* 2019; **15**: 2 [PMID: 30887141 DOI: 10.1186/s40504-019-0091-8]
26 **Kostkova P**. Disease surveillance data sharing for public health: the next ethical frontiers. *Life Sci Soc Policy* 2018; **14**: 16 [PMID: 29971516 DOI: 10.1186/s40504-018-0078-x]
27 **Hand D**, Mannila H, Smyth P. Principles of Data Mining. Cambridge (MA): MIT Press, 2001: 546
28 **Han J**, Kamber M, Pei J. Data mining: Concepts and techniques. In: The Morgan Kaufmann Series in Data Management Systems. 3rd ed. Waltham, 2012
29 **Huang S**, Yang J, Fong S, Zhao Q. Artificial intelligence in cancer diagnosis and prognosis: Opportunities and challenges. *Cancer Lett* 2020; **471**: 61-71 [PMID: 31830558 DOI: 10.1016/j.canlet.2019.12.007]
30 **Liu J**, Pan Y, Li M, Chen Z, Tang L, Lu C, Wang J. Applications of deep learning to MRI images: A survey, in Big Data Mining and Analytics. *Big Data Min Anal* 2018; **1**: 1-18 [DOI: 10.26599/BDMA.2018.9020001]
31 **Topol EJ**. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019; **25**: 44-56 [PMID: 30617339 DOI: 10.1038/s41591-018-0300-7]
32 **Thompson RF**, Valdes G, Fuller CD, Carpenter CM, Morin O, Aneja S, Lindsay WD, Aerts HJWL, Agrimson B, Deville C Jr, Rosenthal SA, Yu JB, Thomas CR Jr. Artificial intelligence in radiation oncology: A specialty-wide disruptive transformation? *Radiother Oncol* 2018; **129**: 421-426 [PMID: 29907338 DOI: 10.1016/j.radonc.2018.05.030]
33 **Li M**, Shen S, Gao W, Hsu W, Cong J. Computed Tomography Image Enhancement Using 3D Convolutional Neural Network. In: Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support. Switzerland: Springer Nature, 2018 [DOI: 10.1007/978-3-030-00889-5_33]
34 **Gupta N**, Kupfer SS, Davis AM. Colorectal Cancer Screening. *JAMA* 2019; **321**: 2022-2023 [PMID: 31021387 DOI: 10.1001/jama.2019.4842]
35 **Lefere P**, Gryspeerdt S, Schotte K. Virtual colonoscopy--an overview. *Onkologie* 2006; **29**: 281-286 [PMID: 16783904 DOI: 10.1159/000093125]
36 **Halligan S**, Altman DG, Taylor SA, Mallett S, Deeks JJ, Bartram CI, Atkin W. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. *Radiology* 2005; **237**: 893-904 [PMID: 16304111 DOI: 10.1148/radiol.2373050176]
37 **Fernández-Esparrach G**, Bernal J, López-Cerón M, Córdova H, Sánchez-Montes C, Rodríguez de Miguel C, Sánchez FJ. Exploring the clinical potential of an automatic colonic polyp detection method based on the creation of energy maps. *Endoscopy* 2016; **48**: 837-842 [PMID: 27285900 DOI: 10.1055/s-0042-108434]
38 **Takemura Y**, Yoshida S, Tanaka S, Kawase R, Onji K, Oka S, Tamaki T, Raytchev B, Kaneda K, Yoshihara M, Chayama K. Computer-aided system for predicting the histology of colorectal tumors by using narrow-band imaging magnifying colonoscopy (with video). *Gastrointest Endosc* 2012; **75**: 179-185 [PMID: 22196816 DOI: 10.1016/j.gie.2011.08.051]
39 **Urban G**, Tripathi P, Alkayali T, Mittal M, Jalali F, Karnes W, Baldi P. Deep Learning Localizes and Identifies Polyps in Real Time With 96% Accuracy in Screening Colonoscopy. *Gastroenterology* 2018; **155**: 1069-1078. e8 [PMID: 29928897 DOI: 10.1053/j.gastro.2018.06.037]
40 **Mori Y**, Kudo SE, Misawa M, Saito Y, Ikematsu H, Hotta K, Ohtsuka K, Urushibara F, Kataoka S, Ogawa Y, Maeda Y, Takeda K, Nakamura H, Ichimasa K, Kudo T, Hayashi T, Wakamura K, Ishida F, Inoue H, Itoh H, Oda M, Mori K. Real-Time Use of Artificial Intelligence in Identification of Diminutive Polyps During Colonoscopy: A Prospective Study. *Ann Intern Med* 2018; **169**: 357-366 [PMID: 30105375 DOI: 10.7326/M18-0249]
41 **Akbari M**, Mohrekesh M, Nasr-Esfahani E, Soroushmehr SMR, Karimi N, Samavi S, Najarian K. Polyp Segmentation in Colonoscopy Images Using Fully Convolutional Network. *Annu Int Conf IEEE Eng Med Biol Soc* 2018; **2018**: 69-72 [PMID: 30440343 DOI: 10.1109/EMBC.2018.8512197]
42 **Renner J**, Phlipsen H, Haller B, Navarro-Avila F, Saint-Hill-Febles Y, Mateus D, Ponchon T, Poszler A, Abdelhafez M, Schmid RM, von Delius S, Klare P. Optical classification of neoplastic colorectal polyps - a computer-assisted approach (the COACH study). *Scand J Gastroenterol* 2018; **53**: 1100-1106 [PMID: 30270677 DOI: 10.1080/00365521.2018.1501092]
43 **Hassan C**, Spadaccini M, Iannone A, Maselli R, Jovani M, Chandrasekar VT, Antonelli G, Yu H, Areia M, Dinis-Ribeiro M, Bhandari P, Sharma P, Rex DK, Rösch T, Wallace M, Repici A. Performance of artificial intelligence in colonoscopy for adenoma and polyp detection: a systematic review and meta-analysis. *Gastrointest Endosc* 2021; **93**: 77-85. e6 [PMID: 32598963 DOI: 10.1016/j.gie.2020.06.059]
44 **Kudo SE**, Misawa M, Mori Y, Hotta K, Ohtsuka K, Ikematsu H, Saito Y, Takeda K, Nakamura H, Ichimasa K, Ishigaki T, Toyoshima N, Kudo T, Hayashi T, Wakamura K, Baba T, Ishida F, Inoue H, Itoh H, Oda M, Mori K. Artificial Intelligence-assisted System Improves Endoscopic Identification of Colorectal Neoplasms. *Clin Gastroenterol Hepatol* 2020; **18**: 1874-1881. e2 [PMID: 31525512 DOI: 10.1016/j.cgh.2019.09.009]
45 **Blanes-Vidal V**, Baatrup G, Nadimi ES. Addressing priority challenges in the detection and assessment of colorectal polyps from capsule endoscopy and colonoscopy in colorectal cancer screening using machine learning. *Acta Oncol* 2019; **58**: S29-S36 [PMID: 30836800 DOI: 10.1080/0284186X.2019.1584404]
46 **Chadebecq F**, Tilmant C, Bartoli A. How big is this neoplasia? *Med Image Anal* 2015; **19**: 58-74

[PMID: 25277373 DOI: 10.1016/j.media.2014.09.002]
47 **Ştefănescu D**, Streba C, Cârţână ET, Săftoiu A, Gruionu G, Gruionu LG. Computer Aided Diagnosis for Confocal Laser Endomicroscopy in Advanced Colorectal Adenocarcinoma. *PLoS One* 2016; **11**: e0154863 [PMID: 27144985 DOI: 10.1371/journal.pone.0154863]
48 **Tamai N**, Saito Y, Sakamoto T, Nakajima T, Matsuda T, Sumiyama K, Tajiri H, Koyama R, Kido S. Effectiveness of computer-aided diagnosis of colorectal lesions using novel software for magnifying narrow-band imaging: a pilot study. *Endosc Int Open* 2017; **5**: E690-E694 [PMID: 28782001 DOI: 10.1055/s-0043-105490]
49 **Brenner H**, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; **383**: 1490-1502 [PMID: 24225001 DOI: 10.1016/S0140-6736(13)61649-9]
50 **Simon K**. Colorectal cancer development and advances in screening. *Clin Interv Aging* 2016; **11**: 967-976 [PMID: 27486317 DOI: 10.2147/CIA.S109285]
51 **Ito N**, Kawahira H, Nakashima H, Uesato M, Miyauchi H, Matsubara H. Endoscopic Diagnostic Support System for cT1b Colorectal Cancer Using Deep Learning. *Oncology* 2019; **96**: 44-50 [PMID: 30130758 DOI: 10.1159/000491636]
52 **Hornbrook MC**, Goshen R, Choman E, O'Keeffe-Rosetti M, Kinar Y, Liles EG, Rust KC. Early Colorectal Cancer Detected by Machine Learning Model Using Gender, Age, and Complete Blood Count Data. *Dig Dis Sci* 2017; **62**: 2719-2727 [PMID: 28836087 DOI: 10.1007/s10620-017-4722-8]
53 **Xu JF**, Kang Q, Ma XY, Pan YM, Yang L, Jin P, Wang X, Li CG, Chen XC, Wu C, Jiao SZ, Sheng JQ. A Novel Method to Detect Early Colorectal Cancer Based on Chromosome Copy Number Variation in Plasma. *Cell Physiol Biochem* 2018; **45**: 1444-1454 [PMID: 29466793 DOI: 10.1159/000487571]
54 **Graham S**, Chen H, Gamper J, Dou Q, Heng PA, Snead D, Tsang YW, Rajpoot N. MILD-Net: Minimal information loss dilated network for gland instance segmentation in colon histology images. *Med Image Anal* 2019; **52**: 199-211 [PMID: 30594772 DOI: 10.1016/j.media.2018.12.001]
55 **Wan N**, Weinberg D, Liu TY, Niehaus K, Ariazi EA, Delubac D, Kannan A, White B, Bailey M, Bertin M, Boley N, Bowen D, Cregg J, Drake AM, Ennis R, Fransen S, Gafni E, Hansen L, Liu Y, Otte GL, Pecson J, Rice B, Sanderson GE, Sharma A, St John J, Tang C, Tzou A, Young L, Putcha G, Haque IS. Machine learning enables detection of early-stage colorectal cancer by whole-genome sequencing of plasma cell-free DNA. *BMC Cancer* 2019; **19**: 832 [PMID: 31443703 DOI: 10.1186/s12885-019-6003-8]
56 **Wang Q**, Wei J, Chen Z, Zhang T, Zhong J, Zhong B, Yang P, Li W, Cao J. Establishment of multiple diagnosis models for colorectal cancer with artificial neural networks. *Oncol Lett* 2019; **17**: 3314-3322 [PMID: 30867765 DOI: 10.3892/ol.2019.10010]
57 **Shahbazy M**, Vasighi M, Kompany-Zareh M, Ballabio D. Oblique rotation of factors: a novel pattern recognition strategy to classify fluorescence excitation-emission matrices of human blood plasma for early diagnosis of colorectal cancer. *Mol Biosyst* 2016; **12**: 1963-1975 [PMID: 27076033 DOI: 10.1039/c6mb00162a]
58 **Liu S**, Zhang Y, Ju Y, Li Y, Kang X, Yang X, Niu T, Xing X, Lu Y. Establishment and Clinical Application of an Artificial Intelligence Diagnostic Platform for Identifying Rectal Cancer Tumor Budding. *Front Oncol* 2021; **11**: 626626 [PMID: 33763362 DOI: 10.3389/fonc.2021.626626]
59 **Gupta P**, Chiang SF, Sahoo PK, Mohapatra SK, You JF, Onthoni DD, Hung HY, Chiang JM, Huang Y, Tsai WS. Prediction of Colon Cancer Stages and Survival Period with Machine Learning Approach. *Cancers (Basel)* 2019; **11** [PMID: 31842486 DOI: 10.3390/cancers11122007]
60 **Weis CA**, Kather JN, Melchers S, Al-Ahmdi H, Pollheimer MJ, Langner C, Gaiser T. Automatic evaluation of tumor budding in immunohistochemically stained colorectal carcinomas and correlation to clinical outcome. *Diagn Pathol* 2018; **13**: 64 [PMID: 30153844 DOI: 10.1186/s13000-018-0739-3]
61 **Borkowski AA**, Wilson CP, Borkowski SA, Thomas LB, Deland LA, Grewe SJ, Mastorides SM. Comparing Artificial Intelligence Platforms for Histopathologic Cancer Diagnosis. *Fed Pract* 2019; **36**: 456-463 [PMID: 31768096]
62 **Hilario M**, Kalousis A. Approaches to dimensionality reduction in proteomic biomarker studies. *Brief Bioinform* 2008; **9**: 102-118 [PMID: 18310106 DOI: 10.1093/bib/bbn005]
63 **Komeda Y**, Handa H, Watanabe T, Nomura T, Kitahashi M, Sakurai T, Okamoto A, Minami T, Kono M, Arizumi T, Takenaka M, Hagiwara S, Matsui S, Nishida N, Kashida H, Kudo M. Computer-Aided Diagnosis Based on Convolutional Neural Network System for Colorectal Polyp Classification: Preliminary Experience. *Oncology* 2017; **93** Suppl 1: 30-34 [PMID: 29258081 DOI: 10.1159/000481227]
64 **Ciompi F**, Geessink O, Bejnordi BE, De Souza GS, Baidoshvili A, Litjens G, van Ginnekan B, Nagtegaal I, Van Der Laak J. The importance of stain normalization in colorectal tissue classification with convolutional networks. *IEEE* 2017; 160-163 [DOI: 10.1109/ISBI.2017.7950492]
65 **Dimitriou N**, Arandjelović O, Harrison DJ, Caie PD. A principled machine learning framework improves accuracy of stage II colorectal cancer prognosis. *NPJ Digit Med* 2018; **1**: 52 [PMID: 31304331 DOI: 10.1038/s41746-018-0057-x]
66 **Ngan TT**, Lan LTH, Tuan TM, Son LH, Tuan LM, Minh NH. Colorectal Cancer Diagnosis with Complex Fuzzy Inference System. In: Frontiers in Intelligent Computing: Theory and Applications. Advances in Intelligent Systems and Computing 2020. Satapathy S, Bhateja V, Nguyen B, Nguyen N, Le DN, editors. Springer, Singapore, 2020 [DOI: 10.1007/978-981-32-9186-7_2]
67 **Hu HP**, Niu ZJ, Bai YP, Tan XH. Cancer classification based on gene expression using neural networks. *Genet Mol Res* 2015; **14**: 17605-17611 [PMID: 26782405 DOI:

10.4238/2015.December.21.33]
68 **Xu G**, Zhang M, Zhu H, Xu J. A 15-gene signature for prediction of colon cancer recurrence and prognosis based on SVM. *Gene* 2017; **604**: 33-40 [PMID: 27998790 DOI: 10.1016/j.gene.2016.12.016]
69 **Zhang X**, Yang Y, Wang Y, Fan Q. Detection of the BRAF V600E Mutation in Colorectal Cancer by NIR Spectroscopy in Conjunction with Counter Propagation Artificial Neural Network. *Molecules* 2019; **24** [PMID: 31208050 DOI: 10.3390/molecules24122238]
70 **Coppedè F**, Grossi E, Lopomo A, Spisni R, Buscema M, Migliore L. Application of artificial neural networks to link genetic and environmental factors to DNA methylation in colorectal cancer. *Epigenomics* 2015; **7**: 175-186 [PMID: 25942531 DOI: 10.2217/epi.14.77]
71 **Kel A**, Boyarskikh U, Stegmaier P, Leskov LS, Sokolov AV, Yevshin I, Mandrik N, Stelmashenko D, Koschmann J, Kel-Margoulis O, Krull M, Martínez-Cardús A, Moran S, Esteller M, Kolpakov F, Filipenko M, Wingender E. Walking pathways with positive feedback loops reveal DNA methylation biomarkers of colorectal cancer. *BMC Bioinformatics* 2019; **20**: 119 [PMID: 30999858 DOI: 10.1186/s12859-019-2687-7]
72 **Ferrari R**, Mancini-Terracciano C, Voena C, Rengo M, Zerunian M, Ciardiello A, Grasso S, Mare' V, Paramatti R, Russomando A, Santacesaria R, Satta A, Solfaroli Camillocci E, Faccini R, Laghi A. MR-based artificial intelligence model to assess response to therapy in locally advanced rectal cancer. *Eur J Radiol* 2019; **118**: 1-9 [PMID: 31439226 DOI: 10.1016/j.ejrad.2019.06.013]
73 **Lisboa PJ**, Taktak AF. The use of artificial neural networks in decision support in cancer: a systematic review. *Neural Netw* 2006; **19**: 408-415 [PMID: 16483741 DOI: 10.1016/j.neunet.2005.10.007]
74 **Kickingereder P**, Isensee F, Tursunova I, Petersen J, Neuberger U, Bonekamp D, Brugnara G, Schell M, Kessler T, Foltyn M, Harting I, Sahm F, Prager M, Nowosielski M, Wick A, Nolden M, Radbruch A, Debus J, Schlemmer HP, Heiland S, Platten M, von Deimling A, van den Bent MJ, Gorlia T, Wick W, Bendszus M, Maier-Hein KH. Automated quantitative tumour response assessment of MRI in neuro-oncology with artificial neural networks: a multicentre, retrospective study. *Lancet Oncol* 2019; **20**: 728-740 [PMID: 30952559 DOI: 10.1016/S1470-2045(19)30098-1]
75 **Yin M**, Ma J, Xu J, Li L, Chen G, Sun Z, Liu Y, He S, Ye J, Mo W. Use of artificial neural networks to identify the predictive factors of extracorporeal shock wave therapy treating patients with chronic plantar fasciitis. *Sci Rep* 2019; **9**: 4207 [PMID: 30862876 DOI: 10.1038/s41598-019-39026-3]
76 **Chen J**, Remulla D, Nguyen JH, Aastha D, Liu Y, Dasgupta P, Hung AJ. Current status of artificial intelligence applications in urology and their potential to influence clinical practice. *BJU Int* 2019 [PMID: 31219658 DOI: 10.1111/bju.14852]
77 **Somashekhar SP**, Sepúlveda MJ, Puglielli S, Norden AD, Shortliffe EH, Rohit Kumar C, Rauthan A, Arun Kumar N, Patil P, Rhee K, Ramya Y. Watson for Oncology and breast cancer treatment recommendations: agreement with an expert multidisciplinary tumor board. *Ann Oncol* 2018; **29**: 418-423 [PMID: 29324970 DOI: 10.1093/annonc/mdx781]
78 **Mayo RM**, Summey JF, Williams JE, Spence RA, Kim S, Jagsi R. Qualitative Study of Oncologists' Views on the CancerLinQ Rapid Learning System. *J Oncol Pract* 2017; **13**: e176-e184 [PMID: 28118106 DOI: 10.1200/JOP.2016.016816]
79 **Schöllhorn WI**. Applications of artificial neural nets in clinical biomechanics. *Clin Biomech (Bristol, Avon)* 2004; **19**: 876-898 [PMID: 15475120 DOI: 10.1016/j.clinbiomech.2004.04.005]
80 **Mitsala A**, Tsalikidis C, Pitiakoudis M, Simopoulos C, Tsaroucha AK. Artificial Intelligence in Colorectal Cancer Screening, Diagnosis and Treatment. A New Era. *Curr Oncol* 2021; **28**: 1581-1607 [PMID: 33922402 DOI: 10.3390/curroncol28030149]
81 **Kim EJ**, Woo HS, Cho JH, Sym SJ, Baek JH, Lee WS, Kwon KA, Kim KO, Chung JW, Park DK, Kim YJ. Early experience with Watson for oncology in Korean patients with colorectal cancer. *PLoS One* 2019; **14**: e0213640 [PMID: 30908530 DOI: 10.1371/journal.pone.0213640]
82 **Miyano S**. [Artificial Intelligence for Cancer Genomic Medicine: Understanding Cancer is Beyond Human Ability]. *Brain Nerve* 2019; **71**: 25-32 [PMID: 30630127 DOI: 10.11477/mf.1416201213]
83 **Aktürk Ü**, Erci B. The Effect of Watson's Human Caring Model on Meaning of Life and Symptom Management in Cancer Patients Undergoing Chemotherapy. *Res Theory Nurs Pract* 2018; **32**: 255-275 [PMID: 30567838 DOI: 10.1891/1541-6577.32.3.255]
84 **Keshava N**, Toh TS, Yuan H, Yang B, Menden MP, Wang D. Defining subpopulations of differential drug response to reveal novel target populations. *NPJ Syst Biol Appl* 2019; **5**: 36 [PMID: 31602313 DOI: 10.1038/s41540-019-0113-4]
85 **Ding D**, Han S, Zhang H, He Y, Li Y. Predictive biomarkers of colorectal cancer. *Comput Biol Chem* 2019; **83**: 107106 [PMID: 31542707 DOI: 10.1016/j.compbiolchem.2019.107106]
86 **Nowak-Sliwinska P**, Scapozza L, Ruiz i Altaba A. Drug repurposing in oncology: Compounds, pathways, phenotypes and computational approaches for colorectal cancer. *Biochim Biophys Acta Rev Cancer* 2019; **1871**: 434-454 [PMID: 31034926 DOI: 10.1016/j.bbcan.2019.04.005]
87 **Horta AB**, Salgado C, Fernandes M, Vieira S, Sousa JM, Papoila AL, Xavier M. Clinical decision support tool for Co-management signalling. *Int J Med Inform* 2018; **113**: 56-62 [PMID: 29602434 DOI: 10.1016/j.ijmedinf.2018.02.014]

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