MINIREVIEWS

Artificial intelligence and cholangiocarcinoma: Updates and prospects

Hossein Haghbin, Muhammad Aziz

Hossein Haghbin, Department of Gastroenterology, Ascension Providence Southfield, Southfield, MI 48075, United States

Muhammad Aziz, Department of Gastroenterology, University of Toledo Medical Center, Toledo, OH 43614, United States

Corresponding author: Hossein Haghbin, MD, Doctor, Department of Gastroenterology, Ascension Providence Southfield, 16001 W Nine Mile Road, Southfield, MI 48075, United States. hoshaq@yahoo.com

Abstract

Artificial intelligence (AI) is the timeliest field of computer science and attempts to mimic cognitive function of humans to solve problems. In the era of "Big data", there is an ever-increasing need for AI in all aspects of medicine. Cholangiocarcinoma (CCA) is the second most common primary malignancy of liver that has shown an increase in incidence in the last years. CCA has high mortality as it is diagnosed in later stages that decreases effect of surgery, chemotherapy, and other modalities. With technological advancement there is an immense amount of clinicopathologic, genetic, serologic, histologic, and radiologic data that can be assimilated together by modern AI tools for diagnosis, treatment, and prognosis of CCA. The literature shows that in almost all cases AI models have the capacity to increase accuracy in diagnosis, treatment, and prognosis of CCA. Most studies however are retrospective, and one study failed to show AI benefit in practice. There is immense potential for AI in diagnosis, treatment, and prognosis of CCA however limitations such as relative lack of studies in use by human operators in improvement of survival remains to be seen.

Key Words: Artificial intelligence; Machine learning; Cholangiocarcinoma; Diagnosis; Treatment; Prognosis

Core Tip: The wide array of modalities available to treat cholangiocarcinoma (CCA) in addition to the diversity of the tumor urges us to use individualized therapy. To establish the proper approach to diagnose, treat, and prognose CCA, analysis of available data is the key to achieve the individualized care. Artificial intelligence can be a potential modality for achieving this goal.

INTRODUCTION

The ever-growing rate of technological advancement in medicine has resulted in the era of "Big data". Artificial intelligence (AI) and its various techniques are used to harness the infinite potential of Big data in medical field[1]. AI, the timeliest field of computer science, involves development of computer algorithms attempting to mimic cognitive function of humans in order to learn and solve problems[2]. Since invention of the first operational computer by Alan Turing in 1940s, we have seen a prodigious rise in AI advancement. Machine learning (ML) is a very practical area of AI that enables computers to learn without direct programming. ML helps machines learn from previous data and improve their learning behavior by gaining experience from data patterns, thereby establishing ever improving predictive models[3]. Various AI techniques including representation learning, natural language processing, and different ML techniques, such as regression trees, support-vector machines (SVM), artificial neural networks (ANN) and more recently, deep learning (DL), have been used in medical field [4]. ML and DL have vastly increased the scope of AI and enabled individualized medicine rather than algorithm-only-based care and has resulted in improved accuracy, efficiency, and outcomes[4].

Despite all the benefits of AI, one should be wary of the drawbacks[5]. The field of AI brings enormous potential however it concurrently brings big ethical problems. ML algorithms, to some extent, function as "black-boxes" where there is difficulty in finding the logic behind the decision by the machine. This will have medicolegal consequences which will be more pronounced as the models become more sophisticated and companies behind ML software reluctant to reveal the details of their software. Moreover, AI poses threats to privacy, data security, and patient autonomy. Lastly, ML algorithms do make mistakes and may not provide accurate results across race, gender, and socioeconomic status spectrum[5].

Cholangiocarcinoma (CCA) is the second most common primary malignancy of the liver. CCA originates from the epithelial cells of the bile ducts exclusive of gallbladder and ampulla of Vater. CCA is an aggressive tumor diagnosed sporadically in advanced stages with high mortality[6]. The incidence of CCA is increasing; therefore, there is increased interest in diagnosis, prognosis, and treatment of this malignancy[7]. Both serum markers and radiologic imaging are used for diagnosis of CCA. A combination of serum markers like liver function tests, carbohydrate antigen (CA) 19-9, and carcinoembryonic antigen (CEA) are utilized to diagnose the disease[8]. The presence of the vast array of serum markers has led to utilization of the markers in novel AI tools in combination with imaging. Positron emission tomography with fluorodeoxyglucose (FDG-PET) integrated with computed tomography (CT) and Magnetic resonance imaging (MRI) in combination with magnetic resonance cholangiopancreatography (MRCP) are valuable tools harnessed by AI to assess the extent of tumor and stage the disease[9, 10]. Treatment includes surgical management, neoadjuvant/adjuvant chemotherapy and chemoradiotherapy, hepatic artery radioembolization, and orthotopic liver transplant in selected patients[11-14]. Endoscopic retrograde cholangiopancreatography (ERCP) has two roles of diagnosis and treatment of CCA. Its diagnostic role includes inspecting and providing samples from the biliary system. As palliative treatment, stent placement provides increased quality of life especially in most unresectable cases[15]. Novel AI tools have been able to help in individualizing candidates for each treatment modality.

Increased mortality from CCA in the last decade has coincided with development of AI technology. Figure 1 illustrates how AI can be used to diagnose, treat, and prognose patients with CCA. This review depicts how AI can analyze the radiologic, serologic, and histologic markers of CCA to diagnose, stage, and aid with an individualized treatment plan in addition to giving a prognostic estimate with or without treatment modalities.

AI has shown promise to aid in diagnosis of CCA. AI is particularly helpful in CCA diagnosis as the condition is not common and there is heterogeneity in anatomical location of the tumor and risk factors of the tumor[16]. This makes the traditional algorithms inferior compared to AI. Many AI tools in the field of ML have been utilized for diagnosis of CCA (Table 1). LR is a linear regression model used for binary classification of problems[17]. SVM is an appropriate model for small samples, high-dimensional,

Table 1 Advantages and disadvantages of artificial intelligence models used for cholangiocarcinoma diagnosis in radiology

AI technology	Imaging modalities used in	Advantages	Disadvantages
Logistic regression	US/CT	Interpretable	Low precision
Support-vector machine	US/CT/MRI	Avoids overlearning and dimension disaster problems	Prone to missing data
Extreme learning machine	CT	Does not need high amount of data for training	Slow processing speed
Artificial neural network	CT/MRI	High generalization power	Needs long training time
Convolutional neural network	US/CT/MRI	Higher efficacy and speed as there is no need to compute features as first step	Needs large training data

AI: Artificial intelligence; CT: Computed tomography; MRI: Magnetic resonance imaging; US: Ultrasound.
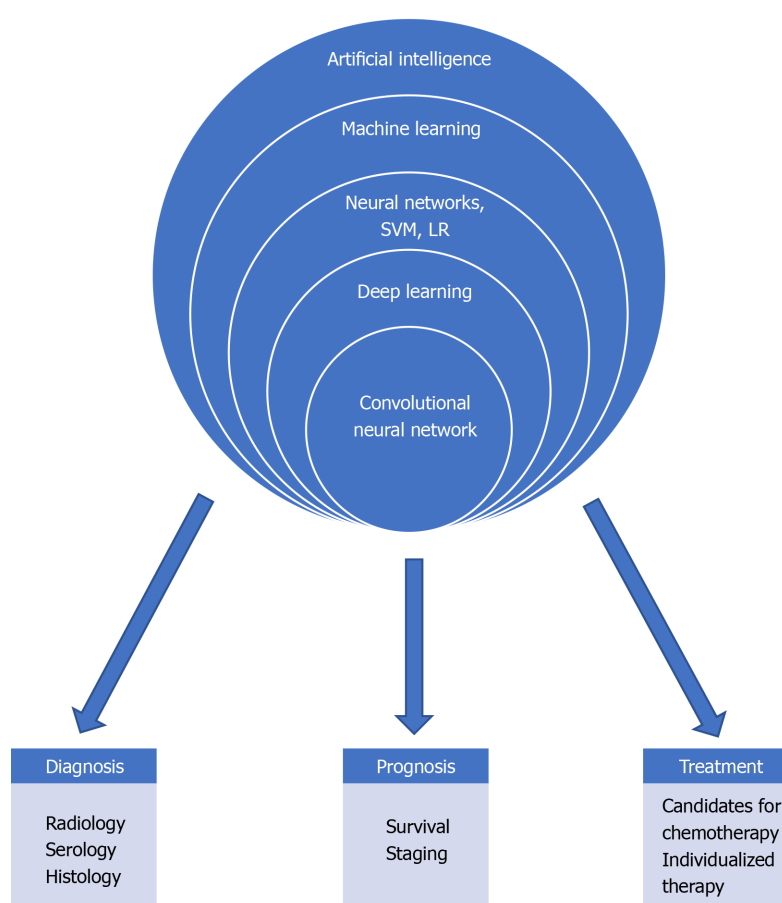

Figure 1 Application of artificial intelligence in addressing cholangiocarcinoma. LR: Logistic regression; SVM: Support-vector machine.

and non-linear patterns assigning labels to objects and has advantage of avoiding "over learning" problem[18]. ANN or multilayer perceptron is an attempt to simulate the biologic nervous system with neurons interconnected able to do parallel processing[17]. Developed by Huang *et al*, Extreme Learning Machines (ELM) are a type of feedforward neural network models that have shown superiority over SVMs and traditional feedforward neural networks[19]. Convoluted neural network (CNN), a type of DL consists of multilayer of ANN that results in a superior learning ability of complex tasks and has been used in radiology and imaging of the malignancy and associating the radiological data to the clinicopathologic data[20,21]. Every method has their advantages and drawbacks illustrated in Table 1.

AI IN THE DIAGNOSIS OF CCA

Serum markers
Evaluation of serum markers is amongst the least invasive and most available data that is present in many patients even before there is a suspicion for diagnosis of CCA. Due to wide availability, these tests are used in adjunct with radiological and other clinical factors in diagnosis of CCA. Sometimes serological models are enough to diagnose the malignancy; for example, Negrini *et al*[22] developed a ML model that analyzed 15 bile acids of the serum and was able to diagnose CCA with good sensitivity of 79% and excellent accuracy, Area Under Curve (AUC), and specificity of 86.4%, 95%, and 100%, respectively. ANN based model using combination CCA associated carbohydrate antigen and alkaline phosphatase showed promise in diagnosing CCA with a sensitivity and specificity of more than 95% [23].

Cytology
ERCP and Cytology of brushings is a valuable tool for diagnosis of CCA. As a common malignant cause of biliary stricture is CCA, cytology can be crucial in early stages of the malignancy when radiology may have limited roles. Urman *et al*[24], using a neural network model studying metabolomic and proteomic profile of bile from 36 CCA patients, was able to satisfactorily distinguish CCA from benign stricture with AUC, sensitivity, and specificity of 98.4%, 94.1% and 92.3%, respectively.

Histology
Histology remains the gold standard for diagnosis of malignancies including CCA. From their Shanghai laboratory, Sun *et al*[25] developed a CNN model for diagnosis of CCA from microscopic hyperspectral pathological slides with promising results. After setting up the first benchmark based on microscopic pathological images consisting of 880 images with pixels manually labeled as tumor or non-tumor for the AI learning, the CNN model was able to diagnose CCA with 88.3% accuracy[25]. AI assistance in histology has not always shown benefits. Stanford University researchers developed an AI diagnostic assistant using DL model to assist pathologists in differentiating hepatocellular carcinoma (HCC) from CCA (26). The model had a good accuracy rate of 84.2% on a set of 80 slides however it failed to improve performance among pathologists [Odds ratio (OR) 1.287, 95%CI: 0.886-1.871]. For all case difficulty levels, the model highly biased the decision of pathologists which led them to wrong diagnosis[26]. The authors concluded that this would question the use of current AI technology for difficult subspecialty tasks[26]. Sometimes CCA can manifest as cancer of unknown primary site (CUP) as it metastasizes to other organs. AI has been used to delineate source of CUP, consisting of 3 to 5% of tumors[27]. CUP-AI-Dx is a CNN model that was trained on more than 18,000 tumors including CCA and has achieved an accuracy of 98.54% in finding the primary site of tumor from the human body system in cross-validation[28].

CT
To elucidate the lesion detected by ultrasound, further workup is required with CT, MRI, and MRCP. As CNN is a DL technique that consists of multilayers of ANN, it has shown great potential especially once it comes to radiology image analysis of pixels. Human yield in diagnosing CCA is limited. Nakai *et al*[29] have developed CNN models factoring in a combination of CT with serum tumor markers including CEA and CA 19-9. Their CNN model was superior to human radiologists in detecting CCA (0.68 *vs* 0.45; *P* = 0.04) [29]. One challenge in diagnosing CCA is differentiating intrahepatic CCA from other intrahepatic malignancies. Xu *et al*[30] have developed an AI model on 28 intrahepatic lymphomas and 101 CCAs. Their model was able to differentiate between the two tumors with AUC and accuracy both more than 85%. Pannoprat *et al*[31] have developed CNN model that can differentiate between CCA and hepatocellular carcinoma (the most common primary liver malignancy) with an 88% accuracy. Zhang *et al*[32] performed a retrospective analysis of contrast enhanced CT of 86 patients with CCA and 46 with combined CCA/HCC tumors, which are difficult to differentiate from CCA necessitating biopsy and surgery. Using ML techniques to classify the lesions as CCA or combined CCA/HCC achieved an AUC of 94.2%[32].

MRI and MRCP
MRI and MRCP have a superior function to diagnose CCA than CT due to ability to illustrate soft tissue, vasculature, and biliary system better than that of CT. ML has been widely utilized in MRI and MRCP. Xu *et al*[33] and Yu *et al*[34] each studied MRI of more than 100 patients with CCA and developed SVM models that showed superiority (validation group AUC 87.0% and 90%, respectively). Logeswaran *et al* [35] in a 2009 study showed 88 to 94% detection rate of Multilayer Perceptron ANN in diagnosis of CCA in MRCP. Yang *et al*[36] developed an AI model for MRI diagnosis and evaluation of extent of lymph node metastasis of CCA patients. After training the model on 100 CCA patients, the model was able to differentiate high *vs* low risk CCA groups and lymph node metastasis with AUCs of 80% and 90% in testing cohorts, respectively[36]. Table 2 lists the studies using AI models to diagnose CCA.

Table 2 Studies utilizing artificial intelligence in the diagnosis of cholangiocarcinoma

Ref.	Year of publication	Title of study	Diagnostic modality	AI model
Chu *et al*[44]	2021	Radiomics using CT images for preoperative prediction of futile resection in intrahepatic cholangiocarcinoma	CT	LR
Ibragimov *et al*[45]	2020	Deep learning for identification of critical regions associated with toxicities after liver stereotactic body radiation therapy	CT	CNN
Liu *et al*[46]	2021	Can machine learning radiomics provide pre-operative differentiation of combined hepatocellular cholangiocarcinoma from hepatocellular carcinoma and cholangiocarcinoma to inform optimal treatment planning?	MRI, CT	SVM
Logeswaran[35]	2009	Cholangiocarcinoma--an automated preliminary detection system using MLP	MRCP	ANN
Midya *et al*[47]	2018	Deep convolutional neural network for the classification of hepatocellular carcinoma and intrahepatic cholangiocarcinoma	CT	CNN
Nakai *et al*[29]	2021	Convolutional neural network for classifying primary liver cancer based on triple-phase CT and tumor marker information: a pilot study	CT, tumor markers	CNN
Negrini *et al*[22]	2020	Machine Learning Model Comparison in the Screening of Cholangiocarcinoma Using Plasma Bile Acids Profiles	Serum bile acids	ML
Pattanapairoj *et al* [23]	2015	Improve discrimination power of serum markers for diagnosis of cholangiocarcinoma using data mining-based approach	Tumor markers	ANN
Peng *et al*[48]	2020	Preoperative Ultrasound Radiomics Signatures for Noninvasive Evaluation of Biological Characteristics of Intrahepatic Cholangiocarcinoma	US	SVM
Peng *et al*[49]	2020	Ultrasound-Based Radiomics Analysis for Preoperatively Predicting Different Histopathological Subtypes of Primary Liver Cancer	US	Radiomics
Ponnoprat *et al*[31]	2020	Classification of hepatocellular carcinoma and intrahepatic cholangiocarcinoma based on multi-phase CT scans	CT	CNN
Selvathi *et al*[50]	2013	Automatic segmentation and classification of liver tumor in CT images using adaptive hybrid technique and Contourlet based ELM classifier	CT	ELM
Sun *et al*[25]	2021	Diagnosis of cholangiocarcinoma from microscopic hyperspectral pathological dataset by deep convolution neural networks	Histology	CNN
Urman *et al*[24]	2020	Pilot Multi-Omic Analysis of Human Bile from Benign and Malignant Biliary Strictures: A Machine-Learning Approach	Bile acids, lipids	ANN
Uyumazturk *et al* [26]	2019	Deep learning for the digital pathologic diagnosis of cholangiocarcinoma and hepatocellular carcinoma: evaluating the impact of a web-based diagnostic assistant	Histology	DL
Wang *et al*[51]	2020	SCCNN: A Diagnosis Method for Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Based on Siamese Cross Contrast Neural Network	CT	ANN
Wang *et al*[52]	2019	Deep learning for liver tumor diagnosis part II: convolutional neural network interpretation using radiologic imaging features	MRI	DL
Xu *et al*[33]	2019	A radiomics approach based on support vector machine using MR images for preoperative lymph node status evaluation in intrahepatic cholangiocarcinoma	MRI	SVM
Xu *et al*[30]	2021	Differentiation of Intrahepatic Cholangiocarcinoma and Hepatic Lymphoma Based on Radiomics and Machine Learning in Contrast-Enhanced Computer Tomography	Contrast enhanced CT	ML
Yang *et al*[36]	2020	Radiomics model of magnetic resonance imaging for predicting pathological grading and lymph node metastases of extrahepatic cholangiocarcinoma	MRI	Radiomics
Yao *et al*[34]	2020	A Novel Approach to Assessing Differentiation Degree and Lymph Node Metastasis of Extrahepatic Cholangiocarcinoma: Prediction Using a Radiomics-Based Particle Swarm Optimization and Support Vector Machine Model	MRI	SVM
Yasaka *et al*[53]	2018	Deep Learning with Convolutional Neural Network for Differentiation of Liver Masses at Dynamic Contrast-enhanced CT: A Preliminary Study	CT	CNN
Zhang *et al*[32]	2020	Differentiation combined hepatocellular and cholangiocarcinoma from intrahepatic cholangiocarcinoma based on radiomics machine learning	CT	Radiomics
Zhao *et al*[28]	2020	CUP-AI-Dx: A tool for inferring cancer tissue of origin and molecular	Tissue biopsy	CNN

		subtype using RNA gene-expression data and artificial intelligence		
Zhou *et al*[54]	2021	Automatic Detection and Classification of Focal Liver Lesions Based on Deep Convolutional Neural Networks: A Preliminary Study	Multiphasic CT	CNN

AI: Artificial intelligence; ANN: Artificial Neural Network; CCA: Cholangiocarcinoma; CNN: Convolutional neural network; CT: Computed tomography; DL: deep learning; ML: machine learning; ELM: Extreme learning machine; LR: Logistic regression; MRCP: Magnetic resonance cholangiopancreatography; MRI: Magnetic resonance imaging; SVM: Support-vector machine, US: Ultrasound.

TREATMENT AND PROGNOSIS OF CCA

ML techniques have also been used for treatment and prognosis of CCA. Almost all studies use a combination of radiological, histological, serological, and clinical data for the best results in predicting the survival of the patients and their response to treatment. Table 3 illustrates the studies using AI models to treat and prognose CCA. The fact that such sophisticated models are needed is proof to the complexity of the CCA pathophysiology and ever developing variety of treatment protocols that makes decision making impossible without help of AI technology. One example of such potential is studied by Tsilimigras *et al*[37]. They constructed a ML model that predicted survival of CCA patients after surgery based on preop serological and radiological data[37]. They conducted an international multi-institutional study on 826 CCA patients, clustering them into groups based on CA 19-9, neutrophil-to-lymphocyte ratio, and tumor size. Their machine learning model showed an excellent agreement with cluster (k = 0.93, 95%CI: 0.90-0.96). This study shows that ML models detect patterns and clusters not detectable to humans using traditional statistical techniques[38]. In this study, AI was able to detect a group of high-risk patients otherwise undetectable. These groups benefit the most from additional neoadjuvant therapy prior to resection as they have a high recurrence[37,38].

CT imaging

Another example of tight interrelation between prognosis and treatment is by Jeong *et al*[39] who elaborated a ML algorithm using the combination of serology, patient characteristics, and CT images of 1421 CCA patients to classify patients to stable and latent risk group. The model was able to predict the disease-free survival between latent and stable groups and response to adjuvant therapy in latent group with excellent ability proven by hazard ratios (HR) of 3.56 and 0.46, respectively ($P < 0.001$ for both) [39]. Tang *et al*[40] drew up a predictive model of CCA survival after studying 101 patients with CCA. Their AI model analyzed radiologic characteristics of the CT scan, tumor markers, and past clinical history like cirrhosis with AUC of 78% and 75% for 3-year and 5-year overall survival, respectively[40].

CA 19-9

CA 19-9 as a tumor marker has shown promise in prognosis of CCA. Li *et al*[41] and Müller *et al*[42] each validated an AI model to prognosticate the CCA tumors based on clinical, tumor markers such as CA 19-9, serologic like albumin level, and clinical data like nodal metastasis. Li *et al*[41] model retrospectively studied a total of 1390 patients and achieved a Concordance Index (C-index) superior to the staging system proposed by the 8th edition of the American Joint Committee on Cancer (C-index: 0.693, 95%CI: 0.663-0.723). Müller *et al*[42] model was able to predict the 1-year survival of patients with an AUC of 89% and 80% for the training and validation sets, respectively.

Palliative measures

Palliative measures like stent placement recommended for inoperable hilar CCAs, are also analyzed by AI models. Shao *et al* developed an ANN model based on data of 288 CCA patients requiring stent placement that can predict stent occlusion with high AUC of 96% (95%CI: 94-99%)[43].

FUTURE DIRECTIONS

The literature review showed a wealth of studies utilizing AI in CCA, however there is room for much improvement. First, there is need for larger prospective studies including different races, nationalities, and socioeconomic statuses to validate role of AI in diagnosis, treatment, and prognosis of CCA. As study from Stanford showed the AI may not prove to be beneficial in all cases in real life; therefore, in some cases there is need for prospective studies showing AI effectiveness in practice[26]. This precaution is accentuated since there was a lack of negative studies in our review of the literature which can potentially bias toward increased efficacy of AI. Furthermore, the prognostic data should be validated by implementing the data into treatment strategies and seeing an increase in not only survival but also quality of life in CCA patients. One last recommendation for medical field is that healthcare professionals' education should be improved to prepare them for the ever-increasing role of AI in daily diagnosis, treatment, and prognosis of CCA and at the same time informing them of the current limits

Table 3 Studies utilizing artificial intelligence in the treatment and prognostication of cholangiocarcinoma

Ref.	Year of publication	Title of study	AI variables	AI model
Jeong *et al*[39]	2020	Latent Risk Intrahepatic Cholangiocarcinoma Susceptible to Adjuvant Treatment After Resection: A Clinical Deep Learning Approach	CT, albumin, platelets, Diabetes, CA 19-9	ML
Ji *et al*[55]	2019	Biliary Tract Cancer at CT: A Radiomics-based Model to Predict Lymph Node Metastasis and Survival Outcomes	CT reported LN features	ANN
Li *et al*[41]	2020	A Novel Prognostic Scoring System of Intrahepatic Cholangiocarcinoma With Machine Learning Basing on Real-World Data	CEA, CA 19-9, tumor stage	ML
Muller *et al* [42]	2021	Survival Prediction in Intrahepatic Cholangiocarcinoma: A Proof-of-Concept Study Using Artificial Intelligence for Risk Assessment	Tumor size, tumor boundary, serology	ANN
Shao *et al*[43]	2018	Artificial Neural Networking Model for the Prediction of Early Occlusion of Bilateral Plastic Stent Placement for Inoperable Hilar Cholangiocarcinoma	Tumor size, nodal involvement	ANN
Tang *et al*[40]	2021	The preoperative prognostic value of the radiomics nomogram based on CT combined with machine learning in patients with intrahepatic cholangiocarcinoma	Tumor size, cirrhosis in CT	Radiomics
Tsilimigras *et al*[37]	2020	A Novel Classification of Intrahepatic Cholangiocarcinoma Phenotypes Using Machine Learning Techniques: An International Multi-Institutional Analysis	Tumor size, nodal involvement, serology	ML

AI: Artificial intelligence; ANN: Artificial Neural Network; CA 19-9: Carbohydrate antigen 19-9; CCA: Cholangiocarcinoma; CEA: Carcinoembryonic antigen; CT: Computed tomography; ML: Machine learning.

and future potentials of the AI technology.

CONCLUSION

In the recent years, we have seen an increase in CCA incidence and, in parallel, a more exponential rise in AI utilization in medicine. AI will be able to utilize the vast amount of data to assist healthcare professionals in addressing CCA. Currently the AI models are showing potential in diagnosis, treatment, and prognosis of CCA. Nonetheless, AI has limits that should be considered; further research is needed to validate use of AI models in real life in use by medical professional to determine their effectiveness and acceptance as auxiliary tools to augment human intelligence. Finally, ethical issues regarding AI including equity and transparency will also need to be addressed to improve acceptance of the technologies by healthcare industry and, more importantly, the patients.

FOOTNOTES

ORCID number: Hossein Haghbin 0000-0001-8947-287X; Muhammad Aziz 0000-0001-5620-8597.

REFERENCES

1   **Hulsen T**, Jamuar SS, Moody AR, Karnes JH, Varga O, Hedensted S, Spreafico R, Hafler DA, McKinney EF. From Big Data to Precision Medicine. *Front Med (Lausanne)* 2019; **6**: 34 [PMID: 30881956 DOI: 10.3389/fmed.2019.00034]

2   **Goodfellow I**, Bengio Y, Courville A.   Deep learning. The MIT Press, 2016 [DOI: 10.1007/s10710-017-9314-z]

3   **Bi Q**, Goodman KE, Kaminsky J, Lessler J. What is Machine Learning? *Am J Epidemiol* 2019; **188**: 2222-2239 [PMID: 31509183 DOI: 10.1093/aje/kwz189]

4   **Kaul V**, Enslin S, Gross SA. History of artificial intelligence in medicine. *Gastrointest Endosc* 2020; **92**: 807-812 [PMID: 32565184 DOI: 10.1016/j.gie.2020.06.040]

5   **Rigby MJ**. Ethical dimensions of using artificial intelligence in health care. *AMA J Ethics* 2019; **21**: E121-E124 [DOI: 10.1001/amajethics.2019.121]

6   **Sirica AE**, Gores GJ, Groopman JD, Selaru FM, Strazzabosco M, Wei Wang X, Zhu AX. Intrahepatic Cholangiocarcinoma: Continuing Challenges and Translational Advances. *Hepatology* 2019; **69**: 1803-1815 [PMID: 30251463 DOI: 10.1002/hep.30289]

7   **Saha SK**, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist* 2016; **21**: 594-599 [PMID: 27000463 DOI: 10.1634/theoncologist.2015-0446]

8   **Malaguarnera G**, Paladina I, Giordano M, Malaguarnera M, Bertino G, Berretta M. Serum markers of intrahepatic cholangiocarcinoma. *Dis Markers* 2013; **34**: 219-228 [PMID: 23396291 DOI: 10.3233/DMA-130964]

9   **Manfredi R**, Barbaro B, Masselli G, Vecchioli A, Marano P. Magnetic resonance imaging of cholangiocarcinoma. *Semin Liver Dis* 2004; **24**: 155-164 [PMID: 15192788 DOI: 10.1055/s-2004-828892]

10 **Corvera CU**, Blumgart LH, Akhurst T, DeMatteo RP, D'Angelica M, Fong Y, Jarnagin WR. 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. *J Am Coll Surg* 2008; **206**: 57-65 [PMID: 18155569 DOI: 10.1016/j.jamcollsurg.2007.07.002]

11 **Horgan AM**, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012; **30**: 1934-1940 [PMID: 22529261 DOI: 10.1200/JCO.2011.40.5381]

12 **Maithel SK**, Gamblin TC, Kamel I, Corona-Villalobos CP, Thomas M, Pawlik TM. Multidisciplinary approaches to intrahepatic cholangiocarcinoma. *Cancer* 2013; **119**: 3929-3942 [PMID: 23963845 DOI: 10.1002/cncr.28312]

13 **Gu J**, Bai J, Shi X, Zhou J, Qiu Y, Wu Y, Jiang C, Sun X, Xu F, Zhang Y, Ding Y. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. *Int J Cancer* 2012; **130**: 2155-2163 [PMID: 21387295 DOI: 10.1002/ijc.26019]

14 **Wu ZF**, Zhang HB, Yang N, Zhao WC, Fu Y, Yang GS. Postoperative adjuvant transcatheter arterial chemoembolisation improves survival of intrahepatic cholangiocarcinoma patients with poor prognostic factors: results of a large monocentric series. *Eur J Surg Oncol* 2012; **38**: 602-610 [PMID: 22417704 DOI: 10.1016/j.ejso.2012.02.185]

15 **Fernandez Y Viesca M**, Arvanitakis M. Early Diagnosis And Management Of Malignant Distal Biliary Obstruction: A Review On Current Recommendations And Guidelines. *Clin Exp Gastroenterol* 2019; **12**: 415-432 [PMID: 31807048 DOI: 10.2147/CEG.S195714]

16 **Kendall T**, Verheij J, Gaudio E, Evert M, Guido M, Goeppert B, Carpino G. Anatomical, histomorphological and molecular classification of cholangiocarcinoma. *Liver Int* 2019; **39** Suppl 1: 7-18 [PMID: 30882996 DOI: 10.1111/Liv.14093]

17 **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]

18 **Noble WS**. What is a support vector machine? *Nat Biotechnol* 2006; **24**: 1565-1567 [PMID: 17160063 DOI: 10.1038/nbt1206-1565]

19 **Huang G**, Huang GB, Song S, You K. Trends in extreme learning machines: A review. *Neural Netw* 2015; **61**: 32-48 [PMID: 25462632 DOI: 10.1016/j.neunet.2014.10.001]

20 **Shen D**, Wu G, Suk HI. Deep Learning in Medical Image Analysis. *Annu Rev Biomed Eng* 2017; **19**: 221-248 [PMID: 28301734 DOI: 10.1146/annurev-bioeng-071516-044442]

21 **LeCun Y**, Bengio Y, Hinton G. Deep learning. *Nature* 2015; **521**: 436-444 [PMID: 26017442 DOI: 10.1038/nature14539]

22 **Negrini D**, Zecchin P, Ruzzenente A, Bagante F, De Nitto S, Gelati M, Salvagno GL, Danese E, Lippi G. Machine Learning Model Comparison in the Screening of Cholangiocarcinoma Using Plasma Bile Acids Profiles. *Diagnostics (Basel)* 2020; **10** [PMID: 32748848 DOI: 10.3390/diagnostics10080551]

23 **Pattanapairoj S**, Silsirivanit A, Muisuk K, Seubwai W, Cha'on U, Vaeteewoottacharn K, Sawanyawisuth K, Chetchotsak D, Wongkham S. Improve discrimination power of serum markers for diagnosis of cholangiocarcinoma using data mining-based approach. *Clin Biochem* 2015; **48**: 668-673 [PMID: 25863112 DOI: 10.1016/j.clinbiochem.2015.03.022]

24 **Urman JM**, Herranz JM, Uriarte I, Rullán M, Oyón D, González B, Fernandez-Urién I, Carrascosa J, Bolado F, Zabalza L, Arechederra M, Alvarez-Sola G, Colyn L, Latasa MU, Puchades-Carrasco L, Pineda-Lucena A, Iraburu MJ, Iruarrizaga-Lejarreta M, Alonso C, Sangro B, Purroy A, Gil I, Carmona L, Cubero FJ, Martínez-Chantar ML, Banales JM, Romero MR, Macias RIR, Monte MJ, Marín JJG, Vila JJ, Corrales FJ, Berasain C, Fernández-Barrena MG, Avila MA. Pilot Multi-Omic Analysis of Human Bile from Benign and Malignant Biliary Strictures: A Machine-Learning Approach. *Cancers (Basel)* 2020; **12** [PMID: 32575903 DOI: 10.3390/cancers12061644]

25 **Sun L**, Zhou M, Li Q, Hu M, Wen Y, Zhang J, Lu Y, Chu J. Diagnosis of cholangiocarcinoma from microscopic hyperspectral pathological dataset by deep convolution neural networks. *Methods* 2021 [PMID: 33838272 DOI: 10.1016/j.ymeth.2021.04.005]

26 **Uyumazturk B**, Kiani A, Rajpurkar P, Wang A, Ball RL, Gao R, Yu Y, Jones E, Langlotz CP, Martin B, Berry GJ, Ozawa MG, Hazard FK, Brown RA, Chen SB, Wood M, Allard LS, Ylagan L, Ng AY, Shen J. Deep Learning for the Digital Pathologic Diagnosis of Cholangiocarcinoma and Hepatocellular Carcinoma: Evaluating the Impact of a Web-based Diagnostic Assistant. *arXiv* 2019; arXiv

27 **Pavlidis N**, Pentheroudakis G. Cancer of unknown primary site. *Lancet* 2012; **379**: 1428-1435 [PMID: 22414598 DOI: 10.1016/s0140-6736(11)61178-1]

28   **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]

29   **Nakai H**, Fujimoto K, Yamashita R, Sato T, Someya Y, Taura K, Isoda H, Nakamoto Y. Convolutional neural network for classifying primary liver cancer based on triple-phase CT and tumor marker information: a pilot study. *Jpn J Radiol* 2021; **39**: 690-702 [PMID: 33689107 DOI: 10.1007/s11604-021-01106-8]

30   **Xu H**, Zou X, Zhao Y, Zhang T, Tang Y, Zheng A, Zhou X, Ma X. Differentiation of Intrahepatic Cholangiocarcinoma and Hepatic Lymphoma Based on Radiomics and Machine Learning in Contrast-Enhanced Computer Tomography. *Technol Cancer Res Treat* 2021; **20**: 15330338211039125 [PMID: 34499018 DOI: 10.1177/15330338211039125]

31   **Ponnoprat D**, Inkeaw P, Chaijaruwanich J, Traisathit P, Sripan P, Inmutto N, Na Chiangmai W, Pongnikorn D, Chitapanarux I. Classification of hepatocellular carcinoma and intrahepatic cholangiocarcinoma based on multi-phase CT scans. *Med Biol Eng Comput* 2020; **58**: 2497-2515 [PMID: 32794015 DOI: 10.1007/s11517-020-02229-2]

32   **Zhang J**, Huang Z, Cao L, Zhang Z, Wei Y, Zhang X, Song B. Differentiation combined hepatocellular and cholangiocarcinoma from intrahepatic cholangiocarcinoma based on radiomics machine learning. *Ann Transl Med* 2020; **8**: 119 [PMID: 32175412 DOI: 10.21037/atm.2020.01.126]

33   **Xu L**, Yang P, Liang W, Liu W, Wang W, Luo C, Wang J, Peng Z, Xing L, Huang M, Zheng S, Niu T. A radiomics approach based on support vector machine using MR images for preoperative lymph node status evaluation in intrahepatic cholangiocarcinoma. *Theranostics* 2019; **9**: 5374-5385 [PMID: 31410221 DOI: 10.7150/thno.34149]

34   **Yao X**, Huang X, Yang C, Hu A, Zhou G, Lei J, Shu J. A Novel Approach to Assessing Differentiation Degree and Lymph Node Metastasis of Extrahepatic Cholangiocarcinoma: Prediction Using a Radiomics-Based Particle Swarm Optimization and Support Vector Machine Model. *JMIR Med Inform* 2020; **8**: e23578 [PMID: 33016889 DOI: 10.2196/23578]

35   **Logeswaran R**. Cholangiocarcinoma--an automated preliminary detection system using MLP. *J Med Syst* 2009; **33**: 413-421 [PMID: 20052894 DOI: 10.1007/s10916-008-9203-3]

36   **Yang C**, Huang M, Li S, Chen J, Yang Y, Qin N, Huang D, Shu J. Radiomics model of magnetic resonance imaging for predicting pathological grading and lymph node metastases of extrahepatic cholangiocarcinoma. *Cancer Lett* 2020; **470**: 1-7 [PMID: 31809800 DOI: 10.1016/j.canlet.2019.11.036]

37   **Tsilimigras DI**, Hyer JM, Paredes AZ, Diaz A, Moris D, Guglielmi A, Aldrighetti L, Weiss M, Bauer TW, Alexandrescu S, Poultsides GA, Maithel SK, Marques HP, Martel G, Pulitano C, Shen F, Soubrane O, Koerkamp BG, Endo I, Pawlik TM. A Novel Classification of Intrahepatic Cholangiocarcinoma Phenotypes Using Machine Learning Techniques: An International Multi-Institutional Analysis. *Ann Surg Oncol* 2020; **27**: 5224-5232 [PMID: 32495285 DOI: 10.1245/s10434-020-08696-z]

38   **Tsilimigras DI**, Paredes AZ, Pawlik TM. ASO Author Reflections: Identification of Intrahepatic Cholangiocarcinoma Clusters Using Machine Learning Techniques: Should Patients be Treated Differently? *Ann Surg Oncol* 2020; **27**: 5233-5234 [PMID: 32591955 DOI: 10.1245/s10434-020-08697-y]

39   **Jeong S**, Ge Y, Chen J, Gao Q, Luo G, Zheng B, Sha M, Shen F, Cheng Q, Sui C, Liu J, Wang H, Xia Q, Chen L. Latent Risk Intrahepatic Cholangiocarcinoma Susceptible to Adjuvant Treatment After Resection: A Clinical Deep Learning Approach. *Front Oncol* 2020; **10**: 143 [PMID: 32140448 DOI: 10.3389/fonc.2020.00143]

40   **Tang Y**, Zhang T, Zhou X, Zhao Y, Xu H, Liu Y, Wang H, Chen Z, Ma X. The preoperative prognostic value of the radiomics nomogram based on CT combined with machine learning in patients with intrahepatic cholangiocarcinoma. *World J Surg Oncol* 2021; **19**: 45 [PMID: 34334138 DOI: 10.1186/s12957-021-02162-0]

41   **Li Z**, Yuan L, Zhang C, Sun J, Wang Z, Wang Y, Hao X, Gao F, Jiang X. A Novel Prognostic Scoring System of Intrahepatic Cholangiocarcinoma With Machine Learning Basing on Real-World Data. *Front Oncol* 2020; **10**: 576901 [PMID: 33552957 DOI: 10.3389/fonc.2020.576901]

42   **Müller L**, Mähringer-Kunz A, Gairing SJ, Foerster F, Weinmann A, Bartsch F, Heuft LK, Baumgart J, Düber C, Hahn F, Kloeckner R. Survival Prediction in Intrahepatic Cholangiocarcinoma: A Proof of Concept Study Using Artificial Intelligence for Risk Assessment. *J Clin Med* 2021; **10** [PMID: 34066001 DOI: 10.3390/jcm10102071]

43   **Shao F**, Huang Q, Wang C, Qiu L, Hu YG, Zha SY. Artificial Neural Networking Model for the Prediction of Early Occlusion of Bilateral Plastic Stent Placement for Inoperable Hilar Cholangiocarcinoma. *Surg Laparosc Endosc Percutan Tech* 2018; **28**: e54-e58 [PMID: 29252936 DOI: 10.1097/SLE.0000000000000502]

44   **Chu H**, Liu Z, Liang W, Zhou Q, Zhang Y, Lei K, Tang M, Cao Y, Chen S, Peng S, Kuang M. Radiomics using CT images for preoperative prediction of futile resection in intrahepatic cholangiocarcinoma. *Eur Radiol* 2021; **31**: 2368-2376 [PMID: 33033863 DOI: 10.1007/s00330-020-07250-5]

45   **Ibragimov B**, Toesca DAS, Chang DT, Yuan Y, Koong AC, Xing L, Vogelius IR. Deep learning for identification of critical regions associated with toxicities after liver stereotactic body radiation therapy. *Med Phys* 2020; **47**: 3721-3731 [PMID: 32406531 DOI: 10.1002/mp.14235]

46   **Liu X**, Khalvati F, Namdar K, Fischer S, Lewis S, Taouli B, Haider MA, Jhaveri KS. Can machine learning radiomics provide pre-operative differentiation of combined hepatocellular cholangiocarcinoma from hepatocellular carcinoma and cholangiocarcinoma to inform optimal treatment planning? *Eur Radiol* 2021; **31**: 244-255 [PMID: 32749585 DOI: 10.1007/s00330-020-07119-7]

47   **Midya A**, Chakraborty J, Pak L, Zheng J, Jarnagin W, Do RK, Simpson AL.   Deep convolutional neural network for the classification of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Proc. SPIE 10575, Medical Imaging 2018: Computer-Aided Diagnosis, 2018: 1057528 [DOI: 10.1117/12.2293683]

48   **Peng YT**, Zhou CY, Lin P, Wen DY, Wang XD, Zhong XZ, Pan DH, Que Q, Li X, Chen L, He Y, Yang H. Preoperative Ultrasound Radiomics Signatures for Noninvasive Evaluation of Biological Characteristics of Intrahepatic Cholangiocarcinoma. *Acad Radiol* 2020; **27**: 785-797 [PMID: 31494003 DOI: 10.1016/j.acra.2019.07.029]

49   **Peng Y**, Lin P, Wu L, Wan D, Zhao Y, Liang L, Ma X, Qin H, Liu Y, Li X, Wang X, He Y, Yang H. Ultrasound-Based Radiomics Analysis for Preoperatively Predicting Different Histopathological Subtypes of Primary Liver Cancer. *Front Oncol* 2020; **10**: 1646 [PMID: 33072550 DOI: 10.3389/fonc.2020.01646]

50   **Selvathi D**, Malini C, Shanmugavalli P.   Automatic segmentation and classification of liver tumor in CT images using adaptive hybrid technique and Contourlet based ELM classifier. 2013 International Conference on Recent Trends in Information Technology (ICRTIT), 2013: 250-256 [DOI: 10.1109/ICRTIT.2013.6844212]

51   **Wang Q**, Wang Z, Sun Y, Zhang X, Li W, Ge Y, Huang X, Liu Y, Chen Y. SCCNN: A Diagnosis Method for Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Based on Siamese Cross Contrast Neural Network. *IEEE Access* 2020; **8**: 85271-85283 [DOI: 10.1109/access.2020.2992627]

52   **Wang CJ**, Hamm CA, Savic LJ, Ferrante M, Schobert I, Schlachter T, Lin M, Weinreb JC, Duncan JS, Chapiro J, Letzen B. Deep learning for liver tumor diagnosis part II: convolutional neural network interpretation using radiologic imaging features. *Eur Radiol* 2019; **29**: 3348-3357 [PMID: 31093705 DOI: 10.1007/s00330-019-06214-8]

53   **Yasaka K**, Akai H, Abe O, Kiryu S. Deep Learning with Convolutional Neural Network for Differentiation of Liver Masses at Dynamic Contrast-enhanced CT: A Preliminary Study. *Radiology* 2018; **286**: 887-896 [PMID: 29059036 DOI: 10.1148/radiol.2017170706]

54   **Zhou J**, Wang W, Lei B, Ge W, Huang Y, Zhang L, Yan Y, Zhou D, Ding Y, Wu J. Automatic Detection and Classification of Focal Liver Lesions Based on Deep Convolutional Neural Networks: A Preliminary Study. *Front Oncol* 2020; **10**: 581210 [PMID: 33585197 DOI: 10.3389/fonc.2020.581210]

55   **Ji GW**, Zhang YD, Zhang H, Zhu FP, Wang K, Xia YX, Jiang WJ, Li XC, Wang XH. Biliary Tract Cancer at CT: A Radiomics-based Model to Predict Lymph Node Metastasis and Survival Outcomes. *Radiology* 2019; **290**: 90-98 [PMID: 30325283 DOI: 10.1148/radiol.2018181408]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com