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**Artificial Intelligence using Advanced Imaging techniques and Cholangiocarcinoma:
Recent advances and future direction**

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Abstract

While cholangiocarcinoma represents only about 3% of all gastrointestinal tumors, it has a dismal survival rate, usually because it is diagnosed at a late stage. The utilization of Artificial Intelligence (AI) in medicine in general, and in gastroenterology has made gigantic steps. However, the application of AI for biliary disease, in particular for cholangiocarcinoma, has been sub-optimal. The use of AI in combination with clinical data, cross-sectional imaging (computed tomography, magnetic resonance imaging) and endoscopy (endoscopic ultrasound and cholangioscopy) has the potential to significantly improve early diagnosis and the choice of optimal therapeutic options, leading to a transformation in the prognosis of this feared disease. In this review we summarize the current knowledge on the use of AI for the diagnosis and management of cholangiocarcinoma and point to future directions in the field.

INTRODUCTION

The concept of AI is best explained as a computer program that possesses the ability to perform functions such as data analysis, learning, and problem solving. Medical artificial intelligence involves the development of AI programs to assist in diagnosis and prognosis, therapeutic decision making, drug development, as

well as development and data mining from the electronic medical records (EMR)^[1-3]. In fact, artificial intelligence is utilized in almost every field of medicine^[4-8], including radiology^[9], gastroenterology^[10], ophthalmology^[11], cardiology^[12], and surgery^[13].

There are many different types of AI. The foundation of the most used form, Artificial Neural Networks (ANN), takes inspiration from the human nervous system^{[1],[3]}. The neurons of ANNs are individual computer processors that interconnect and possess the capability of processing and analyzing large amounts of data^[1]. ANNs are composed of links of multiple layers of these 'neurons', an input layer linked to multiple hidden layers, which are in turn linked to an output layer^[3]. All the layers in an ANN communicate in a feed forward manner with the ability to 'learn' by repeatedly adjusting their links^[2]. Thus, one of the attractive qualities of ANNs is in their analytical and pattern recognition ability. One of the first applications of ANNs in medicine was to aid in the diagnosis of myocardial infarction^[14]. Since that time, ANNs have been widely used¹. Support Vector Machines (SVM) is another type of machine learning which uses data analysis algorithms for classification and regression analysis^[15]. SVMs are widely used in drug development and cancer detection^[16, 17].

Convolutional neural networks (CNN) are a type of deep learning network, a network that incorporates three or more layers, that is commonly employed in medicine, in particular because of its easy applicability to imaging^[18]. Convolutional neural networks are multi-layer analyses which work by taking an image (e.g. from CT, MRI, US) and extracting layers or features at each step of the process. These features are then characterized further by complex mathematical equations to break them down and compare them to similar images, leading to pattern recognition^[18]. CNNs also can place weight on the value of a specific feature, thus allowing for the presence or absence of a given variable to have a greater influence on the overall outcome.

The application of AI has grown at a rapid pace in all fields of medicine, and gastroenterology is no exception^[19]. AI has been utilized in gastroenterology to identify esophageal neoplasms^[20, 21], diagnosis of *Helicobacter pylori*^[22], predict gastric bleeding in patients on anti-thrombotics^[23], predict the length of hospitalization for acute

pancreatitis^[24], differentiate between chronic pancreatitis and pancreatic cancer^[25], stratify the need for ERCP^[26], and characterization of colonic polyps^[27]. These and many other ongoing developments will significantly impact the future of both diagnostic and therapeutic gastroenterology. One area of that has been somewhat neglected in the application of AI in gastroenterology is that of biliary disease, in particular cholangiocarcinoma. In this paper, we will review the current knowledge of the application of artificial intelligence in cholangiocarcinoma and point to the future directions in the field.

CHOLANGIOCARCINOMA

Cholangiocarcinoma (CCA) is a malignant neoplasm that can arise from anywhere along the biliary tree, including within the liver parenchyma, and is classified as distal, perihilar or intrahepatic^[28]. Risk factors for CCA usually include long-term inflammatory states, like those associated with primary sclerosing cholangitis (PSC) and helminthic infection, or the continued presence of choledocholithiasis, but the majority for cases are idiopathic^[29]. Cholangiocarcinoma accounts for about 3% of all gastrointestinal tumors and 10-15% of hepatobiliary tumors^[30]. Although rare, CCA has a very poor prognosis, with 5-year survival rates following surgery rarely exceeding 35%^[21]. Additionally, CCA incidence and mortality rates are increasing worldwide^[31, 32]. CCA is usually detected late in the disease stage and found incidentally due to poor screening methods for early detection^[32]. Early diagnosis is relatively rare, limiting the possibility of curative surgery to <30% of patients^[33]. Furthermore, even among these, about 20-50% of patients deemed candidates for resection *via* preoperative evaluation are found to have unresectable disease burden during surgery^[34, 35].

Given the importance of assessing disease burden, staging and location in determining a patient's treatment plan, it is imperative to have proper preoperative imaging in CCA^[36]. While pathological examination remains the gold standard of diagnosis, grading and staging for CCA, advancements in imaging and detection of biomarkers have paved the way for further preoperative predictability of malignancy type and

responsiveness to therapies. These advancements have allowed for the incorporation of AI into the sphere of cholangiocarcinoma for a more accurate and personalized management of the disease^[37, 38].

ARTICLE IDENTIFICATION PROCESS

The article search process was conducted in Medline and Embase[JM1] . Initial search was using different combinations of keywords such as “cholangiocarcinoma”, “biliary disease”, “cholangioscopy”, “artificial intelligence”, “artificial neural networks” and “convolutional neural networks”. Abstracts of major conferences, such as Digestive Disease Week (DDW) and United European Gastroenterology Week (UEGW) were also reviewed. Finally, a comprehensive search on clinicaltrial.gov was also conducted using the same keywords to search for active clinical trials involving cholangiocarcinoma and artificial intelligence.

ARTIFICIAL INTELLIGENCE IN BILIARY DISEASES AND CHOLANGIOCARCINOMA

Artificial intelligence has been employed to advance the classification and detection of cholangiocarcinoma by aiding in creating a histopathologic database^[39] and characterizing bile acid assays to better predict malignancy^[40]. The use of AI to optimize the predictive value of multivariable models, and in improving the diagnostic yield of cross-sectional imaging and endoscopy has been rapidly expanding. **Table 1** summarizes currently available studies.

Use of artificial intelligence in aiding the predictive abilities of multivariable models

Artificial Intelligence models have been successfully used to improve the predictive abilities of multivariable models both in the pre-interventional diagnostic phase, as well as in post-operative or post-procedural outcomes in CCA patients. Many of these studies has utilized the area under the curve (AUC), the ability of a test to diagnose a

differentiate a disease state from non-disease state, to assess the added benefit of the incorporation of AI in improving the effectiveness of multivariable models.

In the preoperative phase, multiple studies have used AI/radiographic model to predict lymph node metastasis (LNM) in CCA. One study developed and validated a radiographic model for LNM detection in intrahepatic cholangiocarcinoma (ICC) based on computed tomography (CT) imaging features combined with CA19-9 values^[41]. In this study, an acceptable calibration and discrimination was observed in the primary study cohort (AUC 0.8462) and in a validation cohort (AUC 0.8921)^[41]. Another study developed support vector machine model utilizing magnetic resonance imaging (MRI) imaging to preoperatively evaluate for LNM in ICC. This study found that an SVM model combining CA19-9 Levels and select MRI features resulted in better predictive capabilities compared to a model based on imaging features alone (AUC of 0.842 vs. 0.788, $P = 0.0219$)^[42].

One retrospective study was able to use pre-operative MRI combined with post-operative immunohistochemical results to predict early recurrence of ICC after partial hepatectomy^[43]. The model that combined AI with pathology and imaging features had a higher AUC (0.949 v. 0.889, $P = 0.247$) compared to the model that included only the pathology and imaging features, as well as better sensitivity (0.938 vs 0.875), and specificity (0.839 vs 0.774)^[43]. In another study, inclusion of AI improved the ability of a multivariable model to predict early occlusion of bilateral plastic stents placed in patients with inoperable ICC^[44]. In this study, the ANN built with the multivariable model was compared to a multivariable logistic regression model alone that included age, sex, stent diameter, cancer stage, and presence of liver metastasis^[44]. Overall, 288 patients were analyzed, and the ANN model outperformed the logistic regression model (AUC 0.9647 vs. 0.8763, $P = 0.021$)^[44]. Artificial intelligence has also been used to identify which serum biomarkers can have higher diagnostic power for CCA^[45]. An ANN model analyzed eight biochemical markers of CCA in 85 subjects with CCA and in 82 controls^[45]. Alkaline phosphatase and CCA-associated carbohydrate antigen had a higher predictive value for the distinguishing CCA patients from controls^[45]. Finally, in

a recent study, Müller *et al.* developed an ANN utilizing known risk factors for ICC to predict survival in ICC patients. Using 293 patients, the ANN trained model achieved a higher AUC in predicting the 1 year survival rates compared to one of the most commonly used scoring system, the Fudan score (0.89 *vs* 0.77, $P = 0.24$)^[46]. In all of these studies, the addition of AI to commonly used multivariable models significantly improved their predictive abilities, improving therefore the diagnostic and post-procedural management of patient with suspected or diagnosed cholangiocarcinoma.

Use of AI in aiding cross-sectional imaging performance

Artificial Intelligence has been used to aid in the interpretation of cross-sectional imaging for nearly two decades. In a 2006 study, an artificial neural network applied to contrast-enhanced computed tomography (CE-CT) images helped differentiate four types of hepatic masses (intrahepatic peripheral cholangiocarcinoma, hepatocellular carcinoma, hemangioma, and metastatic lesions) from one-another^[47]. The study then employed radiologists to evaluate CT scans with and without the assistance of ANN. There was marked improvement in diagnosis the hepatic masses with assistance from ANN compared to traditional radiologic evaluation (AUC 0.934 *vs* 0.888, $P = 0.02$, respectively)^[47]. Another CT-based study was designed to predict survival outcomes and LNM in biliary tract cancers, and CT images were taken from 177 subjects who had previously undergone surgery^[48]. An ANN based on CT characteristics was then built to classify the subjects into high risk or low risk for lymph node metastasis^[48]. Patients who were classified as high risk based on the ANN model had a significantly lower survival rate compared to those classified as low risk (hazard ratio [HR] 3.37, 95%CI 1.92, 5.91), underlying the importance of AI in improving prediction of disease course after treatment^[48].

Artificial intelligence has also been used with MR imaging (MRI) to improve its diagnostic/predictive power in several studies. One such study investigated the ability for an MRI based AI model to predict LNM in extrahepatic cholangiocarcinoma^[37]. This was a proof-of-concept study to display the viability of a pre-operative prediction of

both LMN and degree of differentiation, which could influence treatment approach. Images from 100 subjects with CCA were analyzed for the degree of CCA differentiation and lymph node metastasis. The AI model had an AUC of 0.9 (95%CI 0.66, 1.0) for predicting LMN while the AUC for degree of differentiation was 0.80 (95%CI 0.58, 0.97)^[37]. In another study, an ANN model based on MRCP images was able to distinguish between patients with CCA from those without CCA^[49]. A total of 309 images were processed, 248 of which were normal and 61 were taken from patient with CCA. The ANN model achieved an accuracy of 94% for distinguishing between them. Furthermore, ANN achieved an accuracy of 88% in distinguishing between images of CCA and images of other common biliary diseases, such as cholecystitis, choledocholithiasis, PSC, and cholangitis^[49].

CHOLEDOCHOLITHIASIS

Artificial intelligence has also been useful for the study of possible risk factors for CCA, such as choledocholithiasis. Several studies have demonstrated that AI can be used to risk-stratify patients with possible choledocholithiasis and therefore aid in the decision-making of the need for ERCP^[54, 55]. One study showed that a machine learning model using pre-ERCP imaging, including US and CT, in addition to select demographic features and laboratory findings can achieve a sensitivity of 97.7% and specificity of 100% in identifying choledocholithiasis^[55]. Another study found that an AI model outperformed ASGE guidelines for proper indication for an ERCP (AUC 0.79 vs. 0.59, respectively)^[54]. In addition, the use of AI would avoid the need for ERCP in 36% of cases who would have undergone the procedure according to the ASGE guidelines^[54]. Once more, the addition of AI can help providers achieve an individualized management program for patients in daily clinical practice.

CONCLUSION

The diagnosis and staging of cholangiocarcinoma is challenging, leading to potential major non-curative surgeries and/or dismal survival rate because of late diagnosis and

inadequate prediction of metastases or recurrence using standard diagnostic methods. The introduction of AI technologies to traditional cross-sectional imaging and endoscopy, can create a major shift in the diagnosis and management of CCA. As mentioned above, many studies have already incorporated AI with significant improvement over traditional clinical data. While most of these studies are retrospective in nature, and therefore provide relatively poor quality data, they are very encouraging.

In addition, new studies are currently ongoing in which AI technologies are used to diagnose and risk-stratify patients with cholangiocarcinoma. The Synergy-AI clinical trial for example, is a non-interventional prospective observational study currently enrolling participants with cholangiocarcinoma, along with other malignancies. This trial is employing an Application Programming Interface to help match participants with personalized treatment protocols based on CT imaging, biomarkers, and laboratory results. In this setting, AI is expected to identify both the most cost effective, appropriate, and personalized treatment approach to each individual's malignancy^[56]. Considering that most hospitals have incorporated electronic medical records (EMR) for their patients, it is easy to see how AI can be used to select different patient variables (biochemical, histological or cross-sectional imaging) and use them to help develop personalized management strategies which optimize outcomes. Combining biomarkers, genetic sequencing, and imaging through AI models could lead to new approaches to the diagnosis and treatment of cholangiocarcinoma, including decreasing the need for unnecessary invasive endoscopic procedures for procurement of biopsies, as well as help develop a more targeted approach for therapy^[57]. While more research and fine tuning of current AI systems is needed before reaching this stage, the future of AI in the management of cholangiocarcinoma seems clearly within reach.

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PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	16 words — 1 %
2	Zolk, Karsten, Oliver Zolk, Thomas Rabenstein, and Karsten Zolk. "Warm water infusion versus air insufflation for aiding colonoscopy insertion", Cochrane Database of Systematic Reviews Protocols, 2012. Crossref	12 words — < 1 %