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Artificial Intelligence Surgery

Review

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Application of artificial intelligence to hepatobiliary cancer clinical outcomes research

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Abstract

The rapid evolution of modern technology has made artificial intelligence (AI) an important emerging tool in healthcare. AI, which is a broad field of computer science, can be used to develop systems or machines equipped with the ability to tackle tasks that traditionally necessitate human intelligence. AI can be used to perform multifaceted tasks that involve the synthesis of large amounts of data with the generation of solutions, algorithms, and decision support tools. Various AI approaches, including machine learning (ML) and natural language processing (NLP), are increasingly being used to analyze vast healthcare datasets. In addition, visual AI has the potential to revolutionize surgery and the intraoperative experience for surgeons through augmented reality enhancing surgical navigation in real-time. Specific applications of AI in hepatobiliary tumors such as hepatocellular carcinoma and biliary tract cancer can improve patient diagnosis, prognostic risk stratification, as well as treatment allocation based on ML-based models. The integration of radiomics data and AI models can also improve clinical decision making. We herein review how AI may be of particular interest in the care of patients with complex cancers, such as hepatobiliary tumors, as these patients often require a multimodal treatment approach.

Keywords: Artificial intelligence, hepatocellular carcinoma, cholangiocarcinoma, outcome research

INTRODUCTION

With the rapid evolution of modern technology, artificial intelligence (AI) has increasingly become integrated into various aspects of human life, particularly the healthcare domain[1,2]. AI, which is a broad field of computer science, can be used to develop systems or machines equipped with the ability to tackle tasks that traditionally necessitate human intelligence[1]. Specifically, AI can be used to perform multifaceted tasks that involve the synthesis of large amounts of data with the generation of solutions, algorithms, and decision support tools[2]. Synthesizing and analyzing large volumes of data, AI can incorporate "unstructured" information including images or text and, in turn, identify a complex interplay among various data points[3,4]. In turn, the integration of AI into healthcare has the potential to yield numerous benefits, including tools to refine patient outcomes, streamline healthcare delivery processes, and inform medical research[5].

AI systems can analyze medical data, such as images, diagnostic tests, and patient records, yielding more accurate tools for diagnosis, as well as prognostically stratifying patients[6,7]. In particular, AI algorithms, which are adept at analyzing large datasets, can identify intricate patterns and trends that are challenging for humans to discern, enabling more accurate identification of disease patterns, as well as prediction of potential health risks. Furthermore, AI holds the promise to prevent or manage diseases more proactively[8,9]. AI can also analyze genetic, clinical, and lifestyle data to facilitate the customization of treatment plans tailored for individual patients[10]. This personalized medicine approach, which more adeptly considers the unique characteristics of each patient, may optimize treatment and increase therapeutic efficacy while minimizing adverse effects. For instance, AI algorithms such as Virtual Twin analysis or Optimal Policy Tree (OPT)[11,12] can differentiate patients into subsets, identifying who may benefit from specific treatment plans, such as upfront surgery versus neoadjuvant or adjuvant chemotherapy[13,14]. Moreover, AI can facilitate drug discovery and selection of chemotherapeutic agents by analyzing massive datasets to predict the most promising drug candidates, as well as potentially optimizing clinical trial designs, thereby reducing the time and cost of developing new drugs to market[15]. Natural Language Processing (NLP) algorithms can also sift through unstructured healthcare data, distilling valuable insights in the electronic health records and medical literature, thus enhancing the accessibility of critical information for healthcare providers and researchers[16]. AI may also help to address healthcare disparities by improving access to medical expertise in underserved or remote areas through AI-powered telemedicine, thereby enabling remote consultations and earlier disease diagnoses[17].

Overall, AI plays a crucial role in healthcare transformation, enhancing diagnostic accuracy, personalizing treatment, expediting research, and enhancing patient care. The ongoing integration of AI technologies holds the promise of revolutionizing healthcare practices and outcomes. AI may be of particular interest in the care of patients with complex cancers such as hepatobiliary (HB) tumors as these patients often require a multimodal treatment approach with surgical resection, as well as therapy with a wide array of different chemotherapy agents[18].

APPLICATION OF AI IN THE MEDICAL FIELD

Different AI approaches to healthcare data

AI can involve various statistical approaches based on different techniques and methodologies. Machine learning (ML) and natural language processing (NLP) are generally among the most used methodologies[19,20]. ML utilizes algorithms and statistical models to refine the performance of designated tasks through experiential learning, while not utilizing explicit factor-based programming. In this way, ML can facilitate the identification of new patterns of knowledge and enhance inferences that enable the forecasting of outcomes or decision tools that are grounded in data. Through the analysis of large amounts of data, ML algorithms facilitate the identification of data patterns and enhance data-based predictions with incrementally improved performance optimization over time. There are various types of ML approaches, such as supervised learning and unsupervised learning[21]. In addition, ML can utilize several different types of algorithms that can recognize patterns within a set of data including artificial neural networks, decision tree algorithms [i.e., random forest (RF), gradient-boosting][22,23], and instance-based algorithms (i.e., support vector machine, k-nearest neighbor)[24,25]. Deep learning (DL) is a subset of ML that involves neural networks with multiple layers (i.e., deep neural networks) and has been demonstrated to be particularly effective in handling complex tasks. DL has gained prominence within the broader field of AI due to its ability to process data in a hierarchical fashion, thereby allowing for more sophisticated and nuanced decision making[26]. DL techniques, particularly convolutional neural networks (CNN), have been applied to radiomics, which is a field of medical imaging that involves extracting a large number of quantitative features from medical images[27]. NLP encompasses the interaction between computers and human language, including tasks such as speech recognition, language translation, sentiment analysis, and language understanding. NLP has given rise to applications such as chatbots, language translation services, and voice-activated assistants[28-30]. NLP enables the handling of vast "unstructured" text-based data, and can enhance the ability to make clinical diagnoses and risk stratification of patients[20,31].

Visual AI

Visual AI involves the utilization of artificial intelligence techniques to analyze and comprehend visual information. Visual AI involves empowering machines to interpret, understand, and make decisions based on visual data (i.e., intraoperative images and videos). Visual AI applications leverage technologies such as computer vision, DL, and various image processing techniques to extract meaningful insights from visual content. The significance of visual AI has gained considerable attention, especially in its potential applications in the field of surgery[32]. For instance, the automation of surgical phase recognition, utilizing AI and computer vision algorithms for image interpretation through DL, has been a subject of recent interest. This application has demonstrated its effectiveness in enhancing surgeon performance in both basic procedures like inguinal hernia repair, as well as complex surgeries such as robot-assisted minimally invasive esophagectomy and hepatectomy[33,34]. In the field of surgical procedures, particularly in liver surgery, in which the understanding of complex anatomy is crucial to improve perioperative outcomes, the implementation of AI as an operative aid is likely to become a hot topic in the future.

Various applications of AI to HB cancer patients

Table 1 summarizes several representative studies related to the application of AI to HB cancer patients.

Hepatocellular carcinoma

Treatment strategies for hepatocellular carcinoma (HCC) are diverse and usually based on factors such as tumor morphology, biology, patient performance status, and background liver condition[35]. The decision-making process becomes even more complex in the retreatment of patients with recurrent lesions post initial liver resection, as many different multidisciplinary approaches need to be considered[36]. To this end, some researchers have sought to establish optimal treatment ML algorithms to inform the care of these patients[37,38]. For example, Famularo *et al*. examined an Italian registry of patients with HCC and an external Japanese cohort to develop and validate a prediction model related to survival after recurrence (SAR)[37]. This model, based on a standard Cox model that incorporated all second-order interactions of treatment with features selected by the Least Absolute Shrinkage and Selection Operator (LASSO)[39], included treatment-related variables and time to recurrence. The resulting ML-based model demonstrated high predictive ability, as shown by the area under the curve (AUC) values (3-year SAR: AUC 0.805; 5-year SAR: AUC 0.785). The authors concluded that an ML-based model could assist in allocating treatment for patients with recurrent HCC[37]. Another study by our own research group utilized an international, multi-

Table 1. Summary of representative studies using machine learning related to hepatobiliary cancers

Ref.	Year	Patient	Clinical application	Machine learning approach
Famularo *et al.*[37]	2022	Hepatocellular carcinoma	Prediction of survival after recurrence	Least Absolute Shrinkage and Selection Operator
Moazzam *et al.*[38]	2024	Hepatocellular carcinoma	Prediction of survival after recurrence	Optimal Survival Tree
Iseke *et al.*[42]	2023	Hepatocellular carcinoma	Prediction of recurrence incorporating MRI data	Conventional neural network
Saillard *et al.*[43]	2020	Hepatocellular carcinoma	Prediction of survival incorporating digitazed histological whole-slide data	Conventional neural network
Jiang *et al.*[49]	2021	Hepatocellular carcinoma	Prediction of microvascular invasion	Radiomics and conventional neural network
Alaimo *et al.*[51]	2023	Intrahepatic cholangiocarcinoma	Prediction of early recurrence	Random forest
Cotter *et al.*[53]	2022	Gallbladder cancer	Prediction of overall survival	Classification and Regression Tree
Tsilimigras *et al.*[54]	2020	Intrahepatic cholangiocarcinoma	Classification based on machine learning	Hierarchical machine-learning
Chen *et al.*[55]	2023	Intrahepatic cholangiocarcinoma	Prediction of very early recurrence	Radiomics and K-means clustering
Alaimo *et al.*[60]	2023	Intrahepatic cholangiocarcinoma	Prediction of survival and recurrence relative to margin width	Optimal policy tree

institutional database to formulate a prediction model for SAR. In this study, the SARScore was proposed as a prediction model based on clinicopathological determinants such as cirrhosis, number of primary tumors, macrovascular invasion, R1 resection margin, alpha-fetoprotein (AFP) > 400 ng/mL on diagnosis of recurrent disease, extrahepatic recurrence, radiologic size and number of recurrent lesions, radiologic recurrent bilobar disease, and recurrence within 24 months after hepatectomy. The clinical applicability of SARScore was assessed using Optimal Survival Tree (OST) analysis[12]. This ML-based tool demonstrated that patients with high SARScores experienced the worst survival outcomes (5-year AUC; training: 0.79 *vs*. testing: 0.71). In turn, the combination of SARScore and OST analysis can provide risk stratification and therapeutic guidance in the treatment of individuals with recurrent HCC.

AI has also been applied to develop prognostic risk scores following hepatectomy[40,41]. Traditionally, prognostic risk stratification has relied on "structured" or pre-specified data including patient characteristics, and tumor size/number. In recent years, AI has evolved to integrate structured information with more detailed yet previously untapped data. For example, Iseke *et al.* employed ML to predict recurrence using pretreatment laboratory, clinical, and magnetic resonance imaging (MRI) data among patients with early-stage HCC initially eligible for liver transplantation[42]. This study demonstrated that combining MRI radiomics with clinical parameters yielded the most accurate prediction of post-treatment recurrence. These data suggested that ML-based models can forecast recurrence before therapy allocation among patients eligible for liver transplantation with early-stage HCC. The incorporation of MRI data into the model significantly enhanced predictive performance compared with reliance on clinical parameters alone. Saillard *et al*. adopted a deep learning technique, utilizing whole-slide digitized histological slides (i.e., whole-slide imaging; WSI) to construct models to predict the survival of HCC patients undergoing surgical resection[43]. Notably, the derived scores demonstrated high C-indexes of 0.78 and 0.75, respectively, outperforming other models using structured clinicopathologic features. AI enabled the exploration of previously untapped data and the identification of distinctive features that may have been overlooked. One significant challenge, however, lies in the external application of imaging-based AI models to other cohorts, as the lack of a user-friendly interface hinders the broad adoption of this technique[44]. Addressing this challenge with the creation of easy-to-use, online applications will be crucial in the future.

Radiomics has emerged as a tool to diagnose, risk stratify, and predict prognosis among patients with HCC[45,46]. For instance, several studies have focused on developing preoperative models to predict microvascular invasion, an important prognostic factor that is traditionally identified only after surgery on pathological examination[47,48]. Jiang *et al*. demonstrated the effectiveness of a ML-based model combining radiomics with other clinicopathologic factors that resulted in high predictive accuracy[49]. In the future, radiomics will likely play a significant role in facilitating decision making regarding the treatment of HCC.

Biliary tract cancer

Bile duct cancer is a rare disease that often poses a diagnostic challenge[50]. To assist in tumor classification and postsurgical prognosis, several researchers have used ML-based approaches to the analysis of international multi-institutional datasets to improve the performance of prognostic tools. For instance, Alaimo *et al*. developed and validated three ML models aimed at predicting early recurrence (within < 12 months after hepatectomy)[51]. Notably, the RF model demonstrated the highest discrimination with an AUC of 0.904 in the training cohort and 0.779 in the validation cohort. The top five influential variables were the tumor burden score[52], perineural invasion, microvascular invasion, carbohydrate antigen (CA)19-9, and nodal status. In a different study by Cotter *et al*., a classification and regression tree (CART) approach was employed to stratify gallbladder carcinoma (GBC) patients relative to OS[53]. Interestingly, CART analysis identified tumor size, biliary drainage, CA19-9 levels, and the neutrophil-lymphocyte ratio (NLR) as the factors most strongly associated with OS, effectively classifying patients into four prognostic groups. Tsilimigras *et al*. utilized ML to classify patients with ICC into three distinctive groups using an unsupervised hierarchical ML technique based on clinicopathologic characteristics: common type, proliferative type, and inflammatory type[54]. Notably, this classification was correlated with survival outcomes with median OS values of 60.4 months for the common type, 27.2 months for the proliferative type, and 13.3 months for the inflammatory type ($P < 0.001$).

Recently, other research teams have examined the integration of radiomics data into prediction models to enhance discrimination ability. For instance, Chen *et al*. incorporated the 3D tumor region of interest (ROI) derived from contrast-enhanced CT to predict very early recurrence of intrahepatic cholangiocarcinoma. In this study, the K-means clustering algorithm was employed to identify novel radiomics-based subtypes of intrahepatic cholangiocarcinoma[55]. Notably, two distinct subtypes based on radiomics features were identified, with subtype 2 tumors demonstrating a higher proportion of very early recurrence (VER) (47.6%) versus subtype 1 lesions (25.5%).

Biliary tract cancer, particularly perihilar cholangiocarcinoma or central-type ICC, often necessitates extensive surgery[56,57]. While major liver resection with vascular resection may lead to a high incidence of morbidity and mortality, patients who require such radical resection might have limited survival benefits, raising questions about the effectiveness of the procedure[58]. To that end, the optimal allocation of treatment in these patients has been a topic of debate. AI has emerged as a possible tool to address this challenge. For example, Ratti *et al*. used an ML algorithm to identify patients most at risk for s "futile" outcomes after surgery for hilar perihilar cholangiocarcinoma defined as severe complications with early recurrence[59]. Of note, independent predictors of futility included an American Society of Anesthesiology (ASA) score ≥ 3, bilirubin at diagnosis ≥ 50 mmol/L, CA 19-9 ≥ 100 U/mL, preoperative cholangitis, portal vein involvement, tumor diameter ≥ 3 cm, and left-sided liver resection. The ML-based scoring system demonstrated good accuracy (AUC 0.755) in the validation cohort. The authors suggested that identifying patients at high risk of "futility" using this AI approach may help guide the consideration of alternative treatment options. In another study, Alaimo *et al*. utilized OPT analysis to define the optimal surgical margin width based on individual clinicopathologic factors[60]. The OPT categorized surgical patients into five groups based on age, tumor size, extent of hepatectomy, and CA19-9 levels. This personalized approach to determining margin width may assist in identifying patients who would benefit most from a wider negative resection margin. Moreover, using such a tool may help avoid unnecessarily wider margins, preventing radical surgery and subsequent surgical morbidity.

Operative aids for HB surgery

AI holds substantial promise in HB surgery, especially related to potential intraoperative support. Previous studies have highlighted the potential usefulness of AI in laparoscopic cholecystectomy[61,62]. For instance, Madani *et al*. demonstrated the efficacy of AI technology employing deep learning algorithms to identify safe and hazardous zones of dissection and other anatomical structures during laparoscopic cholecystectomy, improving the performance of operating surgeons[62]. Intraoperative AI can assist surgeons, particularly trainees, in decision making during surgery and help maintain quality control, as well as facilitate training efficiency.

Accurate assessment of the future liver remnant (FLR) volume is widely acknowledged to reduce the risk of post-hepatectomy liver failure[63]. To mitigate this complication, it is crucial to calculate the precise volume of FLR preoperatively and plan a surgical approach accordingly. Therefore, there is a need to improve conventional methods for this calculation (i.e., contrast-enhanced CT scan). Winkel *et al*. developed a CNN-based algorithm that demonstrated good accuracy, speed, and agreement with manual segmentation[64]. This approach could potentially improve the quality of 3D reconstruction of the liver, which may help more accurately estimate the FLR[65,66]. Incorporating techniques such as augmented reality (AR) and mixed reality allows for the synchronization of 3D-reconstructed images with real-time surgery, representing a safer and more reliable surgical navigation method. Notably, Ntourakis *et al*. reported in a pilot study that AR aided in detecting missing lesions post-chemotherapy for colorectal liver metastases, resulting in a higher likelihood of a margin-negative resection without any local recurrence[67]. The application of AR in robotic hepatectomy also has the potential to enhance a surgeon's ability to achieve a safe tumor resection with an adequate margin[68].

Future perspectives and potential challenges

Looking ahead, the future of AI in healthcare holds promise, yet significant challenges remain. Addressing knowledge gaps surrounding data quality, data governance, interoperability, and algorithm transparency will be paramount. Researchers will need to focus on developing robust frameworks for data integration, standardization, and ethical AI deployment[69]. Additionally, efforts to enhance the interpretability and accountability of AI algorithms will be essential to foster trust among healthcare professionals and patients. The success of AI integration into the clinical setting will be related to external validation in multiple cohorts. In addition, the applicability of AI can be hindered by the dearth of an easy-to-use interface for AI-based models. Over the next five years, we anticipate continued progress in AI-driven diagnostics, personalized medicine, and surgical innovations. However, realizing the full potential of AI in healthcare will require collaborative efforts across academia, industry, and regulatory bodies to ensure responsible and equitable implementation while maximizing patient outcomes.

CONCLUSIONS

Recent advancements in AI offer the chance to enhance the care of patients, as demonstrated in the current study that highlighted the integration of AI into the care of patients with HB tumors. Specifically, AI models have the potential to impact patient stratification and decision making and are poised to become integral components of future surgical research and care. As these technologies continue to evolve, their application could revolutionize medical practices, introducing an era of more precise diagnostics, personalized treatment plans, and innovative approaches to surgical advancements. The fusion of AI and healthcare holds immense promise to optimize patient outcomes, as well as drive transformative breakthroughs in the field.

DECLARATIONS

Authors' contributions

Conceived the idea: Endo Y, Alaimo L, Pawlik TM
Wrote the manuscript: Endo Y, Alaimo L
Reviewed the manuscript: Catalano G, Chatzipanagiotou OP, Pawlik TM

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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