“Artificial intelligence in biliopancreatic endoscopy: Is there any role?”

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Abstract

Artificial intelligence (AI) research in endoscopy is being translated at rapid pace with a number of approved devices now available for use in luminal endoscopy. However, the published literature for AI in biliopancreatic endoscopy is predominantly limited to early pre-clinical studies including applications for diagnostic EUS and patient risk stratification. Potential future use cases are highlighted in this manuscript including optical characterisation of strictures during cholangioscopy, prediction of post-ERCP acute pancreatitis and selective biliary duct cannulation difficulty, automated report generation and novel AI-based quality key performance metrics. To realise the full potential of AI and accelerate innovation, it is crucial that robust inter-disciplinary collaborations are formed between biliopancreatic endoscopists and AI researchers.

Keywords

Artificial Intelligence; Machine Learning; Endoscopic Retrograde Cholangiopancreatography; Endoscopic Ultrasonography;

Introduction

Gastrointestinal endoscopy has some of the most translationally advanced artificial intelligence (AI) applications in medicine. There are multiple regulatory approved devices and published landmark prospective randomised controlled trials for AI in luminal endoscopy [1]. This appears to be a watershed moment for the specialty. However, it is important to recognise that the vast majority of progress has been limited to diagnostic upper and lower gastrointestinal endoscopy. This is primarily due to the identification of optimal use cases, supporting lesion detection and characterisation, where major inter-observer variation exists in routine clinical practice [2].

In comparison to luminal endoscopy, there have been few publications of AI studies related to biliopancreatic endoscopy. It is therefore timely to consider whether AI has a role in biliopancreatic endoscopy and if so, how we can accelerate research in this field by mirroring the successfully translation of AI in luminal endoscopy. This article will provide a narrative review of the existing published literature related to AI in biliopancreatic endoscopy and also consider future directions.

Current Evidence

1) Patient selection

Appropriate risk stratification and selection of patients is critical prior to proceeding to ERCP with therapeutic intent, particularly given the relatively high risk of complications and morbidity when compared with other areas of endoscopy. This is highlighted by the frequently encountered clinical scenario of suspected bile duct stones (choledocholithiasis

(CDL)). Although the advent of less invasive imaging modalities such as Magnetic Resonance Cholangiopancreatography (MRCP) and Endoscopic Ultrasound (EUS) have helped in case selection, this can still represent a challenge.

Several risk prediction models for the presence common bile duct (CBD) stones have been published, with the majority using logistic regression. Jovanovic et al. developed an artificial neural network (ANN) using a dataset of 291 patients who had been prospectively recruited at a single referral centre [3]. All patients underwent ERCP which was considered the diagnostic gold standard. Transabdominal ultrasound was performed to measure the CBD and also determine the presence of hyperechogenic shadow(s). For inclusion, patients needed a firm clinical and/or biochemical suspicion of CDL, such as classical symptoms of right upper quadrant pain and cholestatic liver function tests results. Those with a history of sclerosing cholangitis, prior cholecystectomy and other diseases that could alter imaging and biochemical markers of CDL were excluded. In addition, patients with overt clear signs of cholangitis or pancreatitis were excluded. ERCP demonstrated that 234 (80.4%) patients had positive findings of the presence of CLD without other pathology. A previously established multivariate logistic regression model achieved an area under curve of 0.787, which was significantly outperformed by the ANN model with an area under the curve of 0.884. Furthermore, the ANN correctly identified 92.3% and 69.6% patients with positive and negative findings on ERCP. When considering high risk and low risk groups for CDL the accuracy of the ANN was 92% and 70% respectively. It should be noted however that the study utilised a relatively small dataset, and also is unlikely to be representative of normal clinical practice in that the study group had a higher proportion of positive findings. This study highlights the promise of ANN risk prediction models applied to ERCP but this would require development with much larger datasets and subsequent prospective validation.

<u>Diagnostic EUS</u>

Endoscopic ultrasound can accurately differentiate between pancreatic ductal adenocarcinoma (PDAC) and many benign conditions of the pancreas. However, in certain situations the diagnosis of PDAC can be challenging, particularly in the setting of chronic pancreatitis (CP).

A number of groups have developed computer-aided diagnostic systems, with early retrospective studies using more traditional computer vision and machine learning approaches. The first study using an artificial neural network (ANN) for this indication at EUS was published in 2001, where 21 patients with pancreatic cancer and 14 with chronic pancreatitis based on histology were included [4]. A representative single EUS image was selected for each patient. Similar diagnostic accuracies were reported for the endosonographer at the time of the procedure, a retrospective review by an endosonographer blinded to the clinical information, and the computer diagnosis, achieving 85%, 83% and 80% respectively. At this level of accuracy, the sensitivity for the computer was set at a maximum of 100% and achieved a corresponding specificity of 50%. Another subsequent study utilised an ANN approach for the same clinical problem, extracting the highest quality EUS still images from 22 patients with pancreatic cancer, 12 with chronic pancreatitis and 22 normal [5]. Pancreatic cancer diagnoses were established using EUS-guided FNA, whilst chronic pancreatitis diagnoses were based on clinical presentation and imaging/EUS findings. Following selection of regions of interest (ROIs) on the EUS images, features were extracted and selected for ANN training. The model was able to classify pancreatic cancer with a sensitivity of 93%, specificity of 92%, positive and negative predictive value of 87% and 96% respectively. Meanwhile, a larger study including 332 EUS images (202 pancreatic cancer and 130 non-cancer images from 172 patients) reported that their ANN achieved 87.5% accuracy, 83.3% sensitivity and 93.3% specificity for classifying pancreatic cancer [6]. Of note, the performance improved when images were classified on the basis of patient age.

A different approach, using digital imaging processing based on a support vector machine algorithm, was applied by another research group to 153 pancreatic cancer and 62 non-cancer patients (43 chronic pancreatitis and 20 normal pancreas) [7]. EUS findings were correlated with cytological findings after FNA. ROIs were delineated on still EUS images and texture features were extracted to develop and validate the model which achieved an average accuracy, sensitivity, specificity, positive and negative predictive value of 97.98%, 94.32%, 99.45%, 98.65% and 97.77% respectively for the diagnosis of pancreatic cancer. Another group developed an algorithm using a similar method to create a support vector machine predictive model on a larger dataset of 262 patients with pancreatic cancer and 126 with chronic pancreatitis reporting an average accuracy, sensitivity, specificity, positive and negative predictive value of 94.2%, 96.25%, 93.38%, 92.21% and 96.68% respectively [8].

The application of AI to obtain quantitative assessments and classifications based on a new imaging method, rather than relying on qualitative, subjective assessments by endoscopists, has always been an attractive concept. A prospective, multi-centre, observational trial, evaluated diagnostic performance in 112 patients with pancreatic cancer and 55 with chronic pancreatitis, using EUS guided fine needle aspirations (EUS-FNA), Contrast-enhanced harmonic EUS (CEH-EUS) and ANN classification based on parameters obtained from post-processing of CEH-EUS recordings [9]. The study produced impressive results for the ANN, which demonstrated a sensitivity of 94.64% and specificity of 94.44%, when compared with EUS-FNA (sensitivity 84.82% and specificity 100%) and CEH-EUS (sensitivity 87.5% and specificity 92.72%). The same research group also applied a post-processing ANN analysis to EUS elastography images, initially in a feasibility study involving 68 patients [10]. The ANN was able to differentiate benign from malignant pancreatic with an average testing performance of 95.31% and area under the receiver operating curve of 0.957. A subsequent multicentre study evaluating EUS-elastography in 258 patients (211 with pancreatic cancer and 47 with chronic pancreatitis) demonstrated a superior performance of the ANN (sensitivity 87.59% and specificity 82.94%) when compared to two experienced endoscopists (first reader sensitivity 84.4% and specificity 46.8%, second reader sensitivity 75.4% and specificity 53.2%).

More recently, a deep-learning based approach using a convolutional neural network (CNN) was applied to EUS images, with the aim of improving the diagnosis of autoimmune pancreatitis (AIP) [11]. This retrospective study utilised a database of still images and videos from 583 patients (146 AIP, 292 PDAC, 72 CP and 73 normal pancreas). AIP cases were verified according to the HISORt criteria. PDAC diagnoses were based on cytology/histology, whilst CP and normal pancreas were based on expert opinion. For the video analysis, the CNN was able to distinguish AIP from PDAC with 90% sensitivity and 93% specificity, and overall was 90% sensitive and 85% specific for distinguishing AIP from all studied diagnoses (PDAC,CP and normal pancreas). The authors also conducted an occlusion heatmap analysis to determine key discriminatory features of AIP and PDAC images, such as post-acoustic enhancement deep to a dilated pancreatic duct which was highly predictive of PDAC.

Another retrospective study applied deep learning to EUS images of patients prior to undergoing pancreatectomy for pathologically confirmed intraductal papillary mucinous neoplasms (IPMNs) [12]. A total of 3,970 still EUS images were included from 50 patients (benign IPMN = 27, malignant IPMN = 23) and used for training and evaluating a CNN. The mean AI values (predictive value of malignant IPMN in each image) was 0.808 and 0.104 for malignant and benign IPMNs respectively. Using the AI value, the area under the ROC curve (AUROC) for ability to diagnose malignant IPMNs was 0.91. When a cutoff point of 0.41 was used for AI malignant probability (mean AI value of all images in each patient), the accuracy of the model was 0.94 which was higher than the human pre-operative EUS diagnostic accuracy of 0.56.

Reduced radiation exposure during ERCP

Ionizing radiation remains a central requirement of ERCP, but represents a cumulative risk to the patient, endoscopist, and attending staff. A prospective, non-randomised, non-blinded, study evaluated the ability of an AI-enabled fluoroscopy (AIF) system to reduce radiation exposure during image-guided endoscopic procedures [13]. The AIF system minimises radiation exposure by a secondary collimator by blocking radiation to areas outside the region of interest that the endoscopist is typically focused on during therapeutic image-guided endoscopy. A CNN was trained to identify the ROIs. In the study, 100 consecutive patients were included, alternating between the AIF system and conventional fluoroscopy for image guided endoscopic procedures (>85% ERCP in both cohorts). The ROI was correctly identified using the AIF system in 48 patients, with the other 2 cases needing manual control by the technician. The AIF system resulted in a significantly lower radiation exposure to patients and scatter effect to endoscopists.

Future applications

Whilst there is currently a paucity of published literature and evidence relating to AI in biliopancreatic endoscopy, it is worth exploring where the key principles and concepts could readily translate to other potential use cases.

Cholangioscopy

Endoscopic retrograde cholangiopancreatography (ERCP) remains a central tool in facilitating a pathological diagnosis and delivering therapeutic interventions in the biliopancreatic system. A major drawback of this technique is that it relies on indirect visualization of the bile duct, using fluoroscopic imaging. The diagnosis of lesions (e.g. stones, strictures) and their anatomical location, relies on inexactly targeted sampling, and 2-dimensional imaging, which provide poor sensitivity rates when it comes to diagnosing malignancy [14]. An important step forward has come with the development of improved direct visualization systems - cholangioscopy.

The first commercially available direct visualization system was the so-called mother-baby technique. In this technique, developed in the 1980s, a slim cholangioscope was passed through the working channel of a therapeutic duodenoscope, into the bile duct. This technique requires two endoscopists to control both the cholangioscope and the duodenoscope at the same time. Whilst demonstrating the potential of cholangioscopy the technique did not enter wide use, due to scope fragility and other limitations. In 2005 the first single-operator cholangioscope (SOC) was introduced. The Spyglass Legacy (Boston Scientific, Natick, MA, USA) overcame the limitations of the first mother-baby technique; only one operator was required, and better image quality was achieved, albeit still of only moderate quality. The cholangioscope is passed down the working channel of a standard therapeutic duodenoscope. Development of a digital, single-operator video cholangioscope, with better image resolution and a wider view has been seen with the introduction of the Spyglass DS II cholangioscope (Boston Scientific, Natick, MA, USA) in 2018. Due to its technical improvements and the ability to introduce accessories into the bile duct, the clinical use of peroral cholangioscopy has grown significantly over the past decades. Direct cholangioscopy, using thin nasoendoscopes may also be performed. Although endoscope passed into the biliary tree may be challenging (due in part to biliary intubation from the duodenum) excellent visualisation may be achieved.

In current clinical practice the two main indications for cholangioscopy are the removal of (difficult) bile duct stones and the assessment of indeterminate biliary strictures [15,16]. In patients with difficult bile duct stones (i.e. in whom conventional techniques, such as mechanical lithotripsy or endoscopic papillary large balloon dilatation have failed to allow stone clearance) high success rates are reported for cholangioscopic lithotripsy. According to a review by Karagyozov et al. complete bile duct clearance was achieved in 86 – 97%, with low adverse event rates [17,18] . In the determination of biliary strictures high success rates are reported, with sensitivity and specificity rates for the visual appraisal ranging from 87 – 100% and from 79 – 96%, respectively, and from 58 – 85% and 83 – 100%, respectively, for cholangioscopic intraductal targeted biopsies [19–23]. Although the diagnostic accuracy rates for cholangioscopic intraductal biopsies may be further improved with developments in biopsy forcep capability, more recent studies have shown lower sensitivity and specificity rates for the visual appraisal of biliary strictures than reported previously [24,25]. The significant challenge in the assessment of biliary strictures lies in the differentiation between strictures with abnormal appearing mucosa that are benign, from those that are malignant. Certain diseases, such as primary sclerosing cholangitis (PSC), are predisposed to both benign and malignant stricture formation, and differentiation based on cholangioscopic appearance can be extremely challenging [26]. Certain cholangioscopic features have been reported to be associated with malignant strictures, compared to benign lesions, including neovascularization (dilated tortuous vessels), irregular nodularity, easy oozing or raised lesions [27]. In fact, Kim et al. reported a 100% positive predictive value for dilated tortuous vessels when it comes to detecting malignancy [28]. Recently, Sethi et al. proposed a novel classification system, the ‘Monaco classification’, for the evaluation of biliary strictures [29]. For each visual finding, consensus definitions were achieved, after which eight criteria were developed; ulceration, scaring, papillary projections, presence of a lesion, pronounced pit, abnormal vessels, presence of stricture, and mucosal features. Based on these criteria the experts, who were blinded for additional clinical information, achieved a diagnostic accuracy of 70% in determining a final diagnosis, which is quite promising. However, only considerable inter-observer agreement (IOA) was achieved. In this study, the vast majority of the features achieved only slight to fair IOA, with only one feature having moderate agreement - papillary projections. This is not the only study to report on low IOA for both the cholangioscopic features and the visual diagnosis of the stricture [24,25,30]. Furthermore, features that were previously reported to be consistent with malignancy, such as neovascularization, were not that commonly identified in malignant lesions, and importantly were also identified in benign lesions [24,29]. Therefore, the challenge of the visual appraisal of biliary strictures seems to be twofold. First, the low IOA. In these studies, experts in cholangioscopy participated, yet only slight to fair IOA for the vast majority of the features and for the visual diagnosis was reached. Secondly, features that were thought to be characteristic of malignancy were also identified in benign strictures, which might mean that features of benign and malignant strictures overlap. It is unlikely that the overall disappointing IOA can be attributed to suboptimal visualization, given the recent improvements in the image quality of the cholangioscopes, but it might be explained by subtle differences in the appearance of the features, and importantly by a possible significant overlap in these characteristics between benign and malignant lesions. Developing an international consensus on the appearance of features and the predictive value of different features for malignant or benign lesions might be a solution. However, Sethi et al. have already shown that even after consensus, experts in cholangioscopy only achieve low IOA.

AI could offer a solution by differentiating between benign and malignant features in strictures. Attempts to develop ‘more interpretable’ deep learning models, using techniques such as class activation maps, which aim to identify which regions of images input influence CNNs, could provide interesting insights for diagnostic classification. However, before deep learning solutions can even be considered, it is imperative to develop large, standardised, cholangioscopy video datasets ideally between multiple centres. Advances in AI in the luminal endoscopy field have resulted from the interpretation of thousands of mucosal imaging cases. Due to the recent development of high quality cholangioscopy, and its relatively infrequent use (in comparison with colonoscopy) visual diagnosis studies to date have used only comparatively small numbers (< 100 cases). An additional challenge is the requirement of a robust ‘ground truth’ of a pathological diagnosis against which to set cholangioscopic features. This is usually straight forward in luminal endoscopy, but the suboptimal sensitivity of all non-surgical approaches to making a pathological diagnosis of biliary strictures unavoidably hampers the field. Nevertheless, one might reflect that advances in AI in colonoscopy have resulted from more than 50 years of disease characterisation based on direct mucosal visualisation and sampling. Cholangioscopy has provided this information for barely 10 years.

Prediction of Post ERCP acute pancreatitis

Post ERCP acute pancreatitis (PEP) is the most common complication encountered in practice, with a number of risk factors described in the literature. The development of an accurate and robust prediction score for PEP could allow for more judicious case selection and optimal management to reduce the risk. A machine learning based model has been developed for this purpose and the findings published in abstract form using data from an international, multicentre, prospective study, entitled the 'STARK project' [31]. 1,150 patients were included with an 6.1% incidence of PEP. The model variables that were most relevant included total bilirubin level, body mass index, age, units of alcohol per day, previous sphincterotomy and procedure time. The machine learning model achieved an area under ROC curve of 0.69 and was significantly better than a model based on logistic regression. It is likely that accuracy will improve as machine learning models can be developed in the future using more readily accessible and standardised datasets, ideally captured from routine clinical care.

Bile duct cannulation difficulty prediction

The most fundamental, and at times challenging, action in therapeutic ERCP is selective biliary cannulation. Numerous studies have analysed potential predictive factors associated with success or failure. More recently, a prospective, multi-centre, study validated a novel classification scheme based on the endoscopic appearance of the papilla, demonstrating that cannulation difficulty could be predicted based on visual appearance [32]. The scheme was based on only 4 papilla types. This highlights the frequent challenge with endoscopic classification schemes in achieving a balance between simplicity to achieve widespread clinical use and potential improved diagnostic accuracy with greater complexity that could hinder implementation. Moreover, human derived classification schemes may be a major over-simplification. AI offers a potential solution and could make future 'human' based classification schemes redundant, although once again a robust dataset consisting of papillary images linked to cannulation difficulty and other outcomes would need to be carefully constructed even before preliminary AI studies could begin.

Automated reporting/quality assessment

One of the great proposed benefits of AI for clinicians is the 'gift of time' [33]. Unfortunately, clinicians are facing an increasing administrative burden particularly with the advent of electronic health care records and endoscopy reporting systems requiring increasing data entry. Utilising AI to automatically generate endoscopy reports would be a welcome solution. It has already been demonstrated that AI models can automatically identify key anatomical landmarks in luminal endoscopy, record withdrawal time, quality of bowel preparation and recognise tools [34–36]. Furthermore, computer vision applications can now identify phases of intervention and actions, which will likely translate to automated generation of performance measures for endoscopy quality. For example, adequate documentation of EUS landmarks and bile duct cannulation rate are current key performance measures defined by the European Society of Gastrointestinal Endoscopy (ESGE) that could be routinely captured by AI [37]. Moreover, AI should make us broadly reflect on the limitations of the current defined key performance measures. For instance, pre-clinical studies have evaluated the ability of AI to map the colon during withdrawal that could eventually lead to a novel metric for mucosal inspection [38]. It is noteworthy that few current ERCP performance indicators relate to intra-procedural events, an area that could be revolutionised by the calculation of novel AI-based metrics from routine video analysis.

Next steps and challenges

A translational roadmap for AI in endoscopy has been outlined previously by Mori et al. with current AI polyp detection software in colonoscopy positioned at the very final stages [39]. This pathway will now facilitate the translation of future AI innovations in endoscopy. AI in biliopancreatic endoscopy is at the very early stages of product development and feasibility studies. It is important to recognise that there are major research challenges for AI implementation in endoscopy that have recently been identified [40]. To ensure that AI solutions for bilopancreatic endoscopy are ultimately developed for clinical benefit and to also accelerate translation, the biliopancreatic endoscopic community should form robust inter-disciplinary collaborations particularly with AI researchers in engineering/computer science to address these. For example, current routinely created data from daily endoscopic and clinical practice are largely not available or captured in a standardised format for the purposes of machine learning. In addition, even if data are accessible, the subsequent requirement of expert curation and labelling for the development and validation of AI models represent a major hurdle [41]. This may be a particular challenge for biliopancreatic endoscopy, where data are multimodal, possibly requiring the integrated capture and storage of white light endoscopic images, endoscopic ultrasound and fluoroscopic images along with relevant clinical information. The formation of research consortiums with dedicated infrastructure to handle data sharing and storage between institutions could be critical to help overcome this. It would also be useful to standardise reporting for machine learning models developed in biliopancreatic endoscopy and define expected clinical performance measures so that comparisons are possible and research can lead to advances in the field. It is likely that this will require collaboration and input from professional endoscopy societies. Finally, it is important that the endoscopy community does not get caught up in the hype for AI but recognises that AI may serve as a helpful adjunct to improve clinical practice, rather than a panacea, understanding its potential limitations and recognising that meaningful development of AI could take more time in biliopancreatic endoscopy as compared with luminal endoscopy.

Conclusions

Several applications for AI in biliopancreatic endoscopy have been highlighted, with many more likely to be identified as AI research continues to rapidly expand. AI models could lead to improved patient case selection, prediction of technical or therapeutic difficulty and adverse events. Computer vision-based AI solutions will likely be the first to achieve translation, particularly to improve lesion characterisation in endoscopic ultrasound or cholangioscopy. The use of AI to automatically generate reports and capture quality metrics will likely follow. It is important to recognise that AI research in biliopancreatic endoscopy is at the preliminary stages of translation, consisting of early proof-of-concept or feasibility studies. Successful translation in luminal endoscopy, particularly colonoscopy, has provided a roadmap, emphasising that robust inter-disciplinary collaborations between biliopancreatic endoscopists and AI researchers will accelerate innovation.

Practice Points

- AI is not currently used in widespread routine practice in biliopancreatic endoscopy
- Potential future applications for AI in biliopancreatic endoscopy include patient case selection and risk stratification, lesion characterisation in endoscopic ultrasound or cholangioscopy and automatic report generation with novel quality metrics.

Research Agenda

- The majority of AI studies in biliopancreatic endoscopy are pre-clinical, retrospective studies. Further prospective multi-centre validation studies are needed.
- Robust inter-disciplinary collaborations between computer scientists/engineers and biliopancreatic endoscopists are crucial to achieve successful translation.
- Current important research challenges include data sharing and curation, identifying clear use cases for clinical practice, and defining clinically relevant performance metrics for evaluating AI models.

Conflict of interest

Conflict of interest: none

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