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Role of Artificial Intelligence in Barrett's Esophagus

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Abstract

The application of artificial intelligence (AI) in gastrointestinal (GI) endoscopy has gained significant traction over the last decade. One of the more recent applications of AI in this field includes the detection of dysplasia and cancer in Barrett's esophagus (BE). AI using deep learning methods has shown promise as an adjunct to the endoscopist in detecting dysplasia and cancer. Apart from visual detection and diagnosis, AI may also aid in reducing the considerable interobserver variability in identifying and distinguishing dysplasia on whole slide images (WSI) from digitized BE histology slides. This review aims to provide a comprehensive summary of the key studies thus far as well as providing an insight into the future role of AI in Barrett's esophagus.

INTRODUCTION

"Artificial Intelligence" is a generic term used to denote the ability of a computer program to learn and solve problems autonomously[1]. AI uses input data to learn with the intention of refining the ability to process new data samples that are not part of the original set of training data. This process of "machine learning" (ML) uses mathematical algorithms to capture structure and patterns in large data sets, often in a way that allows the learned function to be applied to new data. Machine learning can be supervised or unsupervised depending on whether the algorithms were trained with known patterns or unknown patterns respectively[2]. Deep learning is a subtype of

machine learning in which a convolutional neural network (CNN) receives input (e.g., endoscopic images), learns specific patterns (e.g., mucosal surface/vascular pattern) and processes this information through the multi-layered network to produce an output (e.g., presence or absence of neoplasia). This form of deep learning algorithm is the main driver for the rapidly advancing role of computer-aided diagnosis (CAD) in detection and characterization of lesions during endoscopy[3].

The greatest impact of AI in GI endoscopy has been made in the area of colonic polyp and adenoma detection[4]. Several clinical studies and meta-analyses have shown the potential and at times, the superiority of AI in colonic adenoma detection rate compared to the endoscopist[5-8]. The crux of AI research in GI endoscopy has focused primarily on three domains which include detection, classification and delineation of lesions or disease entities[9]. There is an increasing amount of research in all three domains with regards to the application of AI in BE.

BARRETT'S ESOPHAGUS

Barrett's esophagus (BE) is defined as a change in the squamous lining of the distal esophagus to metaplastic columnar epithelium with goblet cells[10]. This is typically associated with chronic gastroesophageal reflux disease (GERD) with as much as 12% of patients with GERD symptoms harboring BE[11]. While there are variances in how BE is defined between different guidelines[12-14], there is definitive data that it is a precursor that increases the risk of esophageal adenocarcinoma (EAC)[15]. Hence early detection of dysplasia within BE is crucial to institute definitive treatment where possible and prevent further progression into neoplasia. However, this remains a challenge as endoscopic changes indicating dysplasia or early neoplasia can be subtle and be easily missed[16]. Even when there is no visible dysplasia and biopsies are done as per the Seattle protocol, sampling error can lead to areas of concern being missed[17]. The endoscopic diagnosis of BE dysplasia is generally a two-step process of primary detection in overview, followed by detailed inspection of these visible abnormalities for characterization[18]. This process relies on the individual experience of the endoscopist,

which might further introduce variations and bias, leading to misjudgment and potentially delay in diagnosis and treatment.

Initially there was great interest in image enhancement technologies to overcome these challenges but to date only virtual and dye based chromoendoscopy have met the parameters outlined in American Society for Gastrointestinal Endoscopy's (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI). Specific to BE imaging[19], PIVI recommends that imaging technology with targeted biopsies should have a per-patient sensitivity of 90% or greater and a specificity of 80% or higher to allow reduction in the number of biopsies.

AI has since emerged as a promising adjunct on this front. AI uses various ML algorithms including CNN to identify and process real time endoscopic data to overcome the inherent limitations of an endoscopist.

AIM OF REVIEW

This review will provide a comprehensive summary of the present evidence, recent research advances and future perspectives regarding the utility of AI in BE endoscopy. AI may overcome the human limitations related to poor intra- and inter-observer agreement, a burden that affects many aspects of medical imaging and endoscopy. If a CAD system was to be trained to distinguish between neoplastic and non-neoplastic BE macroscopically on endoscopy and microscopically on histology with almost-perfection, it seems logical these limitations can be overcomed and better tailored medical management can be rendered.

METHODS AND LITERATURE SEARCH

A comprehensive electronic literature search was performed in the PubMed, MEDLINE and EMBASE databases from inception to the 1st September 2022 using the following key search terms "artificial intelligence" OR "AI" OR "convolutional neural network"

OR "deep learning" OR "computer-aided detection" OR "computer-aided diagnosis" AND "Barrett's esophagus." The search was limited to human studies.

Titles and abstracts were screened to exclude studies that did not address the purpose of this review article. The titles of all the identified studies were screened by two reviewers (TNCH and RR) to exclude studies not related to the study topic. The full texts of the screened studies were then assessed for inclusion. Review articles and letters to the editor were excluded. Studies that used other endoscopic techniques such as volumetric laser endomicroscopy were also excluded. Any disagreements were resolved through discussion with senior author LJW until consensus was achieved.

Eligible studies including 12 meta-analyses which reported the use of AI in Barrett's endoscopy and histopathology were included in the review. The analysis flow chart of the included studies is shown in **Figure 1**.

EXISTING DATA ON THE UTILITY OF AI IN BARRETT'S ESOPHAGUS
IDENTIFICATION AND CLASSIFICATION OF BARRETT'S ESOPHAGUS

Pan *et al*[20] developed a DL algorithm using 443 endoscopic images from 187 patients to automatically identify and segment the gastroesophageal junction and squamous-columnar junction of BE. The performance of this automated segmentation algorithm demonstrated satisfactory agreement with expert annotations as measured by intersection over union (IOU) This study demonstrates the potential of DL in automating the identification and the classification of BE according to the Prague C&M classification[21] while reducing the inter-observer variability.

DETECTION OF DYSPLASIA AND ADENOCARCINOMA

Following successful identification and classification of BE, the subsequent detection of dysplasia or EAC can be clinically challenging, particularly for non-experts[22]. Further differentiation between non-dysplasia, low-grade dysplasia, high-grade dysplasia and

EAC can be subjective and difficult when a focal lesion has been detected. Ebigbo et al[23] managed to demonstrate that a CAD system using deep learning of still images (248 high-definition white light images and 74 narrow band images (NBI)) from two databases, was able to diagnose EAC with sensitivity of 97% and 92% as well as specificity of 88% and 100% for white light images (WLI) in both databases respectively. Additionally, the CAD system was able to achieve sensitivity of 94% and specificity of 80% for NBI images. This study demonstrated that a CNN algorithm was able to accurately identify EAC in still endoscopic images, all validated by expert pathologists, at a sufficiently high sensitivity and specificity to meet the PIVI standards mentioned previously.

Due to the limitations of using still endoscopic images, further steps were taken to validate the AI system in real-time by assessing captured endoscopic images taken by an expert BE endoscopist to differentiate between EAC and normal BE with a sensitivity and specificity of 83.7% and 100% respectively with an overall accuracy of 89.9%[24].

Concurrently, de Groof et al[25] conducted a pilot study to develop a CAD system using white light endoscopic images from 60 patients to delineate between BE neoplasm and non-dysplastic BE. One endoscopic image from each patient was included in the CAD system with per-image analysis demonstrating sensitivity of 95%, specificity of 85% and diagnostic accuracy of 91.7%. The CAD system was not only able to delineate a BE neoplastic lesion but also able to indicate the most abnormal area within that delineation to obtain a targeted biopsy. Additionally, it took an average of 1.051 s for the algorithm to analyze an endoscopic image and subsequently produce its lesion delineation, signaling the potential to be used in a real-time, automated setting.

The same group of investigators went on further to develop a deep-learning CAD system for primary detection of neoplasia in patients with BE using a CNN model. The system was initially pretrained with a large dataset of 494364 Labeled endoscopic images from multiple locations of the GI tract using a supervised learning approach. The system was then subsequently trained with BE-specific endoscopic images containing a total of 1544 images of BE neoplasia and non-dysplastic BE before being

validated using two separate external datasets. The CAD system managed to classify images as containing neoplasms or non-dysplastic BE with 89% accuracy, 90% sensitivity and 88% specificity. Performance was also benchmarked against 53 general endoscopists with a wide range of experience. When compared to the endoscopists, the CAD system managed to achieve higher diagnostic accuracy of 88% *vs* 73%, sensitivity of 93% *vs* 72% and specificity of 83% *vs* 74%[26]. Apart from the large databases used to develop and validate the CNN based algorithm, the computational speed per image analysis was 0.24 s which was a significant improvement from their previous CAD system, paving the way for the incorporation of the CAD system during live endoscopic procedures to help delineate BE neoplastic lesions.

For further validation, the CAD system was tested during live endoscopic procedures in 10 patients with non-dysplastic BE and 10 patients with confirmed BE neoplasia. White light endoscopic images were obtained at every 2 cm level of the Barrett's segment and analyzed by the CAD system. The per-level analysis was 90% accurate with a 91% sensitivity and 89% specificity[27], highlighting the comparable diagnostic performance of the CAD system in both real-time and "offline" settings.

Another study also utilized image databases to develop an AI algorithm using 132 high-definition white light endoscopic images from 46 Lesions of histologically confirmed Barrett's neoplasia and 119 images on non-dysplastic Barrett's from 20 patients. The images were used for training, validation and testing of a CNN algorithm to detect Barrett's neoplasia with a sensitivity of 93%, specificity of 78% and accuracy of 83%[28].

The utility of AI in CAD of BE neoplasia was further highlighted in another pilot study, in which Hashimoto *et al*[29] developed a CNN algorithm using 916 images of histology-proven early BE neoplasia containing high-grade dysplasia or T1 stage adenocarcinoma and 919 control images of BE without high-grade dysplasia. The trained CNN algorithm managed to correctly detect early neoplasia in a total of 458 test images with sensitivity of 96.4%, specificity of 94.2% and accuracy of 95.4%.

With the widespread use of image enhanced endoscopy like NBI in routine endoscopic practice for further lesion characterization, it is only natural that a deep learning

algorithm would be developed to interpret NBI images and to aid in the diagnosis of BE neoplasia. A study was conducted using a trained CAD system to interpret 183 NBI zoom images and 157 NBI zoom videos with similar diagnostic accuracy of 84-85%[30].

As most AI studies were largely image database studies and relatively small in number, a meta-analysis of the studies on the performance of AI in detection and characterization of upper GI neoplasia was performed by Arribas *et al*, which included nine studies[22-26,28,31-33] on BE neoplasia detection (total of 12909 images from 1506 patients used for training and a total of 2340 images from 445 patients used for testing). The pooled sensitivity and specificity of BE neoplasia detection was 89% and 88% respectively[34].

A more recent meta-analysis of twelve studies[22,24-28,30,35-39] was conducted to evaluate the diagnostic performance of AI in detecting BE neoplasia comprising 1361 patients and utilizing 532328 images for training. Pooled sensitivity was 90.3% while pooled specificity was 84.4%. Further subgroup analysis demonstrated that pooled sensitivity and specificity were also similar in six studies that used WLI as the main mode of modality[40]. An interesting observation from the meta-analysis was that there was significant heterogeneity amongst the included studies with I^2 of >50% but the area under the summary of receiver operating characteristics curve was 0.94 (95%CI: 0.92-0.96). Upon further assessment of these studies, multiple factors such as the definitions of dysplastic Barrett's, the different types of AI algorithm and imaging modality used are very likely to contribute to the heterogeneity of the study outcome. This highlights the importance for further standardization of future study protocols with regards to the definition of BE neoplastic lesions and imaging modality used.

PREDICTION OF SUBMUCOSAL INVASION IN BARRETT'S ESOPHAGUS

Apart from detection and classification of neoplasia in BE, the application of AI has shown promise in predicting submucosal invasion in Barrett's cancer. The identification of submucosal invasion (T1b) in Barrett's cancer is important as it has implications for the choice of treatment. Lesions with suspected submucosal invasion should be treated

with endoscopic submucosal dissection (ESD) instead of the conventional endoscopic mucosal resection (EMR). ESD is a viable alternative to surgery and considered curative if the resected specimen fulfills the necessary criteria including submucosal invasion depth <500 μm, good to moderate differentiation and no lympho-vascular invasion[13,41] A retrospective, multicenter study was conducted to evaluate the diagnostic performance of a CNN based algorithm using a total of 230 white-light endoscopic still images to discriminate between mucosal (T1a) and submucosal (T1b) Barrett's cancer. The trained AI algorithm was able to predict submucosal invasion and differentiate between T1a and T1b carcinoma with a sensitivity of 77%, specificity of 64% and an accuracy of 71%. The AI algorithm demonstrated comparable performance to five international Barrett's expert endoscopists who evaluated the same set of images[42]. This study brings to light the potential for AI to support the clinical decision-making process with regards to the endoscopic *vs* surgical resection of precancerous lesions by predicting the submucosal invasion in Barrett's cancer.

ARTIFICIAL INTELLIGENCE IN BARRETT'S HISTOPATHOLOGY

Interobserver agreement between pathologists can be variable with regards to interpretation of BE histology, a recognized issue particularly for low grade dysplasia (LGD) and indefinite dysplasia (IND)[43]. A study showed that concordance between pathologists progressively decreased from non-dysplastic BE (79%), high grade dysplasia (71%), LGD (42%) to IND (23%)[44]. Given that a diagnosis of dysplasia has significant implications on surveillance schedule and BE therapy, American College of Gastroenterology recommends confirmation by a second GI pathologist for dysplasia of any grade detected on biopsy [12].

Attempts have been made to use AI to complement the pathologist and improve interpretation of BE histology. It has been made possible with the rapid advancement in the field of digital pathology and the subsequent incorporation of image analysis using AI. Since the introduction of commercial digital slide scanners, it was possible to digitize glass histology slides into whole-slide images (WSI), to facilitate slide-sharing

and clinical discussion, archiving of digitized slides and extraction of histopathological features using deep learning methods for image analysis[45].

A study utilized an attention-based CNN algorithm to analyze BE and esophageal adenocarcinoma using high-resolution WSI and achieved a mean classification accuracy of 83%[46]. Similarly, another study trained and validated a deep learning model using WSI from 542 patients that managed to demonstrate sensitivity and specificity >90% at the various grades of dysplasia (non-dysplastic BE, LGD and HGD)[47]. In time, we expect more studies and advances in this field that can improve interpretation of BE histology with reproducible reliability.

FUTURE PERSPECTIVES OF ARTIFICIAL INTELLIGENCE IN BARRETT'S ESOPHAGUS

GI endoscopy has seen remarkable progress throughout the last few decades with incremental step-wise progress through incorporation of breakthrough technology and medical device innovation. AI has the potential to push the innovation boundary of GI endoscopy by leveraging on existing and new information as well as vast databases to formulate algorithms, and to support the clinician in identifying and characterizing suspicious lesions. In practice, live upper endoscopic images can be sent locally or remotely to the AI system and be analyzed in real time. Based on the available data and capability, the system will be able to detect suspicious lesions for neoplasia and alert the endoscopists to those lesions either with a screen alert or location box. The endoscopist can then decide on the management of the highlighted lesion based on the characterization provided by the system.

AI can lead to earlier detection of neoplasia in BE, improvement in prognosis and reduction of mortality due to EAC. AI in BE is still in its infancy and there is no long-term data to determine the impact of AI on reduction of EAC incidence and EAC-related mortality[48]. But it is not difficult to envision that early and correct staging of neoplasia will spare the patient from the grueling experience of esophageal surgery and will enable the possibility of minimally invasive endoscopic treatments. Additionally,

as described above, the invasion of depth of detected lesions could be characterized with a higher level of confidence, in particular among less experienced endoscopists, in the differentiation between mucosal and submucosal invasion. This has therapeutic consequences in the endoscopic resection approach; EMR *vs* ESD. The studies described were summarized in **Table 1**.

AI has also the potential to reduce inter-observer variability in interpretation of not only endoscopic images but also of high-resolution, digitized histology slides to ascertain presence of dysplasia or EAC, thereby alleviating the burden of having a second pathologist for confirmation. As AI systems develop and assimilate into clinical practice, it becomes imperative that they are tested and validated in real-world settings, in diverse patient populations, with physicians of varying expertise, with different endoscope types and in different practice settings. There has been a proposal by ASGE AI task force to develop a large open-source image library as a resource to validate AI systems and to moderate data variability[49].

It is also conceivable that a trained AI system will also be able to generate an endoscopy report at the end of a session, including automated Prague C&M measurements, measurements of hiatal hernia and so on to be reviewed by the endoscopist for verification. Extending beyond that, AI has the potential, *via* a subtype of deep learning called natural language processing (NLP)[50,51], to automatically extract and analyze keywords from free-text endoscopic and pathology reports, potentially aiding the physician to diagnose, plan and to recommend the appropriate endoscopic surveillance intervals for patients with BE.

CONCLUSION

AI has made significant progress in diagnostic endoscopy and in the identification of BE pathology using a digital workflow. AI driven systems are likely to become an important tool to detect and to characterize Barrett's esophagus related dysplasia and early adenocarcinoma as they can present as very subtle lesions on endoscopy. Further

development and validation are required before AI can be adopted mainstream in the clinical management of BE.

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