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Review Article

How Far Will Clinical Application of AI Applications Advance for Colorectal Cancer Diagnosis?

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Abstract
Integrating artificial intelligence (AI) applications into colonoscopy practice is being accelerated as deep learning technologies emerge. In this field, most of the preceding research has focused on polyp detection and characterization, which can mitigate inherent human errors accompanying colonoscopy procedures. On the other hand, more challenging research areas are currently capturing attention: the automated prediction of invasive cancers. Colorectal cancers (CRCs) harbor potential lymph node metastasis when they invade deeply into submucosal layers, which should be resected surgically rather than endoscopically. However, pretreatment discrimination of deeply invasive submucosal CRCs is considered difficult, according to previous prospective studies (e.g., <70% sensitivity), leading to an increased number of unnecessary surgeries for large adenomas or slightly invasive submucosal CRCs. AI is now expected to overcome this challenging hurdle because it is considered to provide better performance in predicting invasive cancer than non-expert endoscopists. In this review, we introduce five relevant publications in this area. Unfortunately, progress in this research area is in a very preliminary phase, compared to that of automated polyp detection and characterization, because of the lack of number of invasive CRCs used for machine learning. However, this issue will be overcome with more target images and cases. The research field of AI for invasive CRCs is just starting but could be a game changer of patient care in the near future, given rapidly growing technologies, and research will gradually increase.

Keywords
machine learning, colonoscopy, computer-aided diagnosis, colorectal cancer

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Introduction

Colonoscopy, combined with adenoma removal, reportedly contributes to the reduction of both the incidence and mortality of colorectal cancers (CRCs)[1,2]. Therefore, removal of all the neoplastic lesions is strongly encouraged in most clinical guidelines. There are generally two kinds of removal methods: endoscopic resection and surgical resection. From the histopathological perspective, adenomas and slightly invasive (<1000 μm) submucosal CRCs (T1 CRCs) should be resected endoscopically, while deeply invasive T1 CRCs and CRCs, invading muscle layer or deeper, should be resected surgically. This is because the latter lesions have the potential to metastasize, while the former ones have very few risks of metastasis. Therefore, predicting the invasion depth of T1 CRCs would be the key challenge for most endoscopists.

However, pre-surgical discrimination of T1 CRCs is very

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Table 1. Reports on Automated Prediction of Invasive Colorectal Cancer.

Reference	Year	Endoscopic modality	Study design	Subjects	Outcomes
Tamai et al. [11]	2017	Magnifying NBI	Retrospective study	121 lesions	83.9% sensitivity and 82.6% specificity for adenomas and deeply invasive submucosal cancer, respectively
Stefanescu et al. [19]	2016	Confocal laser endomicroscopy	Retrospective study	155 images	84.5% accuracy
Takeda et al. [16]	2017	Endocytoscopy	Retrospective study	200 images	89.4% sensitivity and 98.9% specificity for adenomas
Ito et al. [17]	2019	White light endoscopy	Retrospective study	190 images	67.5% sensitivity and 89.0% specificity for deeply invasive submucosal cancer (cross validation)
Lui et al. [18]	2019	White light endoscopy and non-magnifying NBI	Retrospective study	76 lesions	88.2% sensitivity and 77.9% specificity for endoscopically curative lesions

Note: NBI, narrow-band imaging

challenging[3,4]. According to a multicenter, randomized controlled trial, conducted by Shimura et al., use of magnified chromoendoscopy (i.e., pit pattern diagnosis) helped endoscopists identify the deeply invasive T1 CRCs with 74.2% sensitivity and 68.6% specificity[5]. Similarly, another prospective trial, conducted by Backes et al., revealed 63.3% sensitivity and 99.0% specificity in identifying deeply invasive T1 CRCs under observation with narrow-band imaging (NBI, Olympus Corp. Tokyo, Japan)[6]. These two prospective studies support the fact that roughly 30% of deeply invasive T1 CRCs are misdiagnosed as slightly invasive CRCs, leading to two-step therapies, namely endoscopic resection followed by adjuvant surgeries. Furthermore, low specificity in the prediction of deeply invasive T1 CRCs may result in unnecessary surgeries for slightly invasive T1 CRCs. Therefore, there are many clinical management issues for T1 CRCs due to the lack of high-performance optical diagnosis.

To overcome this challenge in colonoscopy practice, the use of artificial intelligence (AI) to help estimate invasive cancer has recently gained considerable attention. AI tools based on machine learning algorithms can theoretically learn patterns in cancer appearance and leverage them to classify CRCs optically[7]. Until the early 2010s, research on this topic was limited to mainly computer-vision fields because of the lack of computer power and robustness of the developed algorithms. However, with the advent of deep learning models and outstanding computer power improvement (*e.g.*, use of graphics processing units for machine learning), AI is now being implemented in colonoscopies. Three AI tools for colonoscopy, developed for polyp detection and characterization, have already secured regulatory approval and, thus, can be used freely in clinical practice[8-10]. However, research progress for automated invasive cancer prediction is in a very preliminary phase compared to that of automated polyp detection and characterization because the number of invasive cancers is far lower than that of colorectal polyps. There are only five publications devoted to predicting invasion depth of CRCs, all of which are non-prospective, experimental, small studies (Table 1). In this review, we share AI tools' potential for estimating T1 CRCs' invasion depth by introducing these publications. We guess the accumulation of the target images and cases in the near future will compensate for the current lack of evidence in this field.

Prediction of Cancer Invasion with Magnified NBI

Magnifying NBI is the most eagerly investigated modality to construct a cancer prediction algorithm. Tamai et al. first reported that the AI tool might identify deeply invasive T1 CRCs using this widely available NBI technology[11]. They developed an AI algorithm, based on a handcrafted feature extraction, focusing on superficial vessels' morphologies, and validated its ability using 121 images from 121 lesions as the test set. The AI model could classify images with Sano's colorectal magnifying NBI classification[12] into three categories (1, capillary pattern(CP) type I; 2, CP type II + CP type IIIA; 3, CP type IIIB), which correlated with non-neoplastic polyps, adenomas, and slightly invasive T1 CRCs, and deeply invasive T1 CRCs, respectively. The developed model achieved 84% sensitivity and 83% specificity in discriminating deeply invasive T1 CRCs. This performance seems to be outstanding considering even experts reportedly achieved 74% sensitivity and 69% specificity in recognizing deep T1 invasion in a randomized controlled trial[5]. The notable limitation, however, is that determination of region of interest (ROI) was conducted not automatically, but manually by a single experienced endoscopist, which means selection bias was not eliminated.

Prediction of Cancer Invasion with Confocal Laser Endomicroscopy

Contact endomicroscopy is an attractive, advanced imaging modality for predicting lesion pathology because it can visualize in vivo cancer cell in real time. There are two contact endomicroscopes commercially available: probe-based confocal laser endomicroscopy (p-CLE, Cellvizio, Mauna Kea) and endocytoscopy (CF-H290ECI, Olympus). These exciting modalities have also been attractive AI targets because contact microscopy can help overcome practical issues of magnifying endoscopy, which always requires adjusting the depth of the focus and determining the ROI manually; contact endomicroscopes allow focused, fixed-size images, which can help provide smooth image analysis. In addition, they do not require endoscopists to pick up the ROI since the images obtained with p-CLE or endocytoscopy are exactly the ROI of the targeted lesions.

p-CLE allows the endoscopist to obtain real-time, in vivo "optical biopsies" with 1000-fold magnification. To obtain the cellular images, intravenous injection of a fluorescence prior to observation is mandatory because it enhances the blood flow, which indirectly enhances the cellular structure.

Stefanescu et al. reported an AI tool designed for p-CLE; in this study, they evaluated 725 images using 155 different test materials in an experimental fashion. The constructed model provided was 85% accurate in differentiating CRCs from background mucosa. Unlike the study by Tamai et al., they did not evaluate the AI's capability to discriminate the T1 CRCs' invasion depth. The developed model's diagnostic algorithm was based on k-nearest neighbor classification and neural network analysis. Handcrafted features, such as anatomical feature identification, were extracted and used for the machine learning process.

Prediction of Cancer Invasion with Endocytoscopy

Endocytoscopy enables in vivo observation of cancer cells and superficial vessels at the microscopic level (approximately ×500 magnifying capability) under methylene blue staining and NBI, respectively. By Researchers at Showa University in Japan have eagerly explored implementing AI technologies. Notably, the AI tool designed for endocytoscopy, with a function of identifying neoplastic changes in colorectal polyps, cleared regulatory approval from the Japanese regulatory body in 2018 and is now in the market (EndoBRAIN; Cybernet, Tokyo)[8,13-15]. Furthermore, the research team investigated the possibility of identifying CRCs[16]. A benchmark test, reported by Takeda et al., showed that a modified AI algorithm successfully identified cancerous change, with sensitivity of 89% and specificity of 99%. This study, however, was also a retrospective, experimental study, investigating only 200 images as the test set; therefore, prospective evaluation is indispensable.

Prediction of Cancer Invasion with White Light Endoscopy

AI for white light endoscopy, the most common endoscopic modality, has not been investigated as extensively in the field of colonoscopy, probably because white light endoscopy images are thought to provide limited information compared to other more advanced imaging modalities. However, two research teams explored this uncultivated area with use of deep learning technologies.

Ito et al. developed a deep learning-based algorithm to identify deeply invasive T1 CRCs and evaluated its performance using 190 endoscopic images in a retrospective manner[17]. Their model provided 67.5% sensitivity and 89.0% specificity for deeply invasive T1 CRCs under the cross validation methodology. This performance, however, did not significantly exceed expert endoscopists' performance[5,6]; thus further algorithm improvement and more robust evaluation, such as prospective studies, are expected as a next step.

Lui et al. also developed a similar model based on a deep learning algorithm[18]. This study was the gold standard for machine learning. They set endoscopically curative resection as the AI prediction target, which was defined as histology no more advanced than well-differentiated adenocarcinoma, ≤1 mm submucosal invasion, and no lymphovascular invasion. In other words, they did not target simply invasion depth but more practical and relevant pathological features. The developed model was validated using 76 large colorectal lesions as a test set (56 were endoscopically curable lesions, and 20 were endoscopically incurable lesions). The model, based on white light endoscopy imaging, provided 78.2% sensitivity and 72.6% specificity for endoscopically curative lesions. Its performance was in line with the previous study by Ito et al. However, their model, based on non-magnified NBI images, provided outstanding diagnostic abilities of 94.6% sensitivity and 92.3% specificity. Given its excellent performance under the NBI mode, this may replace the conventional diagnostic method for large colorectal neoplasms, which requires experience and expertise. Of course, prospective evaluation is mandatory before implementation. These kinds of benchmark tests are always accompanied by considerable selection bias, which hinders study result generalization.

Conclusions

AI can be a promising tool to standardize colonoscopy practice, which inherently harbors a risk of misestimating invasive cancers. The increased number of publications in

this field demonstrates progress toward the widespread use of AI in colonoscopy practice. However, it is crucial to interpret the study design and results of recent publications carefully; the supporting evidence on the efficacy of AI in predicting invasive cancer is currently very weak because of the absence of prospective studies. This suggests the currently available evidence is likely to overestimate AI's performance. Thus, prospective trials in which the AI technologies are used in real-time fashion is strongly desired to explore "real" AI performance in a real-world practice before implementing the technology. Considering the difficulty in prospectively accumulating enough number of T1 CRCs to meet the study outcome measures, international, multicenter trials would be required. With these issues appropriately addressed, we guess AI could be a game changer for managing T1 CRCs.

Conflicts of Interest

YM, and MM received speaking honoraria from Olympus Corp.

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