Response to the Reviews

Dear Editor and Reviewers,

On behalf of my coauthors, we are grateful to you for giving us an opportunity to revise our manuscript. We greatly appreciate the editor and reviewers for their positive and constructive comments and suggestions on our manuscript, entitled "Artificial intelligence and early esophageal cancer" (Manuscript NO: 70270). We have studied the comments carefully and have made corrections that we hope meet with your approval. Attached, please find the revised version (all changes are marked in red and underlined), which we would like to submit for your kind consideration. We would like to express our great appreciation to you for providing comments on our paper.

Looking forward to hearing from you. Thank you and best regards.

Yours sincerely,

M.D., Ph.D., Shizhu Jin.

Responses to Reviewer 1

Q1. A very good review paper in the discipline that puts significance of researching the development of CAD frameworks using deep learning for the more accurate and efficient diagnosis of early EC with the help of large sample data centers.

Response: Thank you very much for your review and approval of our article, and for giving this review the opportunity to be published in Artificial Intelligence in Gastrointestinal Endoscopy magazine.

Responses to Reviewer 2

First of all, thank you very much for your constructive and insightful criticism and advice. We addressed all the points raised by the reviewer as summarized below.

Q1. Introduction: Adding clear aims/objectives.

Response: Thank you for your valuable suggestion. We rewrote the "Introduction" part of the manuscript to make it clearer and clarify the aims at the end. Barrett's esophagus (BE) is a premalignant condition characterized by the replacement of columnar epithelium with esophageal squamous epithelium. Esophageal cancer (EC) is the seventh most common cancer and the sixth leading cause of cancer-related mortality worldwide[1]. EC mainly consists of two histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the main pathological type in Asian countries, and the 5-year survival rate is less than 20%[2]. EAC is more common in Western countries, and its incidence has been on the rise globally in recent years[3]. The development of esophageal cancer (EC) from early to advanced stages is accompanied by a high mortality rate and poor prognosis. Early detection and diagnosis greatly impact the prognosis of EC. The need for more efficient detection methods for early EC has led to in-depth research in the field of artificial intelligence (AI). The purpose of this review is to summarize the diagnostic value of AI for BE and early EC, which is conducive to the early treatment of patients and the reduction in mortality. In this review, we will discuss the following: (1) the utility of AI techniques in the endoscopic detection of BE; (2) the utility of AI techniques in the endoscopic detection of early EC; (3) problems and prospects of AI-assisted endoscopic diagnosis. We have modified the manuscript. Please refer to lines 61-78 on page 5.

INTRODUCTION

Barrett's esophagus (BE) is a premalignant condition characterized by the replacement of columnar epithelium with esophageal squamous epithelium. Esophageal cancer (EC) is the seventh most common cancer and the sixth leading cause of cancer-related mortality worldwide[1]. EC mainly consists of two histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the main pathological type in Asian countries, and the 5-year survival rate is less than 20%[2]. EAC is more common in Western countries, and its incidence has been on the rise globally in recent years[3]. The development of esophageal cancer (EC) from early to advanced stages is accompanied by a high mortality rate and poor prognosis. Early detection and diagnosis greatly impact the prognosis of EC. The need for more efficient detection methods for early EC has led to in-depth research in the field of artificial intelligence (AI). The purpose of this review is to summarize the diagnostic value of AI for BE and early EC, which is conducive to the early treatment of patients and the reduction in mortality. In this review, we will discuss the following: (1) the utility of AI techniques in the endoscopic detection of BE; (2) the utility of AI techniques in the endoscopic detection of early EC; (3) problems and prospects of AI-assisted endoscopic diagnosis.

Q2. A paragraph on methods; covering how did they collect and systematise the information in their abstract and after introduction in the main manuscript.

Response: Thank you for raising this issue, it is our negligence not to make it clear in the manuscript. We found that based on deep learning (DL) and convolutional neural network (CNN) methods, the current computer-aided diagnosis (CAD) system has gradually developed from in vitro image analysis to real-time detection and diagnosis. We have modified the "Abstract" part of the manuscript. Please refer to lines 39-42 on page 3. In addition, after introduction in the main manuscript, we also added methods to each author's research. Please refer to lines 138-139, 142 on page 7; 152-153 on page 8; 187 on page 9; 254 on page 11; 279-280 on page 12; 295 on page 13; 323 on page 14; 360 on page 15; 369, 395 on page 16.

recent research on AI and early EC. We found that based on deep learning (DL) and convolutional neural network (CNN) methods, the current computer-aided diagnosis (CAD) system has gradually developed from in vitro image analysis to real-time detection and diagnosis. Based on powerful

van der Sommen *et al*[23] collected 100 images from 44 BE patients and created a ML algorithm called Support Vector Machine (SVM), that employed specific texture and color filters to detect early neoplasia in BE. The sensitivity and specificity of the system were 83% for the per-image analysis and 86% and 87% for the per-patient analysis, respectively.

Maarten *et al*[24] developed a CAD system based on a CNN model that was first trained with 494364 images and then further trained with 690 BE neoplasia and 557 nondysplastic Barrett's esophagus (NDBE) WLI images.

de Groof *et al*[25,26] developed a CAD system based on ResNet/U-Net model to help endoscopists detect early BE neoplasia. The system was trained

de Groof *et al*[29] designed a ML algorithm called SVM based on WLI images from 40 BE neoplasias patients and 20 NDBEs patients. All of the

Ohmori *et al*[41] developed a CAD system based on CNN to evaluate the diagnosis of ESCC under ME and non-ME. The researchers used 7844 ME and

Kumagai *et al*[43] constructed an AI model based on CNN with GoogLeNet to judge benign and malignant endocytoscopic system (ECS) images with different degrees of magnification. The AI system was trained

Guo *et al*[44] developed a CAD system based on CNN for the real-time detection of precancerous lesions and ESCC. A total of 6473 NBI images were

Tokai *et al*[46] collected 1751 ESCC images to design an AI diagnostic system using CNN techniques. The system used DI technology to evaluate the

Uema *et al*[50] constructed a CNN (ResNeXt-101) model to classify ESCC microvessels. The study used 1777 ESCC images under ME-NBI as a training

Fukuda *et al*[51] developed a CNN-based CAD system to diagnose ESCC. The researchers used 23746 ESCC images (1544 patients) and 4587

Waki *et al*[53] constructed an AI system based on CNN with 17336 images of ESCC (1376 patients) and 1461 images of noncancerous/normal esophagi (196 patients). While recording the verification video, the endoscopic operator

Q3. Abstract should holt titles; Background, Aims, methods, findings and conclusions.

Response: Thank you for your valuable advice for improving the manuscript. Due to the magazine required an unstructured abstract, we put the parts together. Now we have modified the abstract to make its parts clearer. In this review, we aimed to provide a comprehensive overview of how AI can help doctors diagnose early EC and precancerous lesions and make clinical decisions based on the predicted results. We analyzed and summarized the recent research on AI and early EC. We found that based on deep learning (DL) and convolutional neural network (CNN) methods, the current computer-aided diagnosis (CAD) system has gradually developed from in vitro image analysis to real-time detection and diagnosis. Based on powerful computing and DL capabilities, the diagnostic accuracy of AI is close to or better than that of endoscopy specialists. We also analyzed the shortcomings in the current AI research and corresponding improvement strategies. We believe that the application of AI-assisted endoscopy in the diagnosis of early EC and precancerous lesions will become possible after the further advancement of AI-related research. Please refer to lines 27-48 on page 3.

Abstract: The development of esophageal cancer (EC) from an early to an advanced stage results in a high mortality rate and poor prognosis. Advanced EC not only poses a serious threat to the life and health of patients but also places a heavy economic burden on their families and society. Endoscopy is of great value for the diagnosis of EC, especially in the screening stage of Barrett's esophagus (BE) and early EC. However, at present, endoscopy has a low diagnostic rate for early tumors. In recent years, artificial intelligence (AI) has made remarkable progress in the diagnosis of digestive system tumors, providing a new model for clinicians to diagnose and treat these tumors. In this review, we aimed to provide a comprehensive overview of how AI can help doctors diagnose early EC and precancerous lesions and make clinical decisions based on the predicted results. We analyzed and summarized the recent research on AI and early EC. We found that based on deep learning (DL) and convolutional neural network (CNN) methods, the current computer-aided diagnosis (CAD) system has gradually developed from in vitro image analysis to real-time detection and diagnosis. Based on powerful computing and DL capabilities, the diagnostic accuracy of AI is close to or better than that of endoscopy specialists. We also analyzed the shortcomings in the current AI research and corresponding improvement strategies. We believe that the application of AI-assisted endoscopy in the diagnosis of early EC and precancerous lesions will become possible after the further advancement of AI-related research.

Q4. Lot many ahort setences such as 'EC progresses rapidly and has a poor prognosis', needs revision and rewrite.

Response: We greatly appreciate your careful review of our manuscript. We have revised the manuscript accordingly. The development of esophageal cancer (EC) from an early to an advanced stage results in a high mortality rate and poor prognosis. Please refer to lines 27-48 on page 3 and 69-70 on page 5.

Abstract: The development of esophageal cancer (EC) from an early to an advanced stage results in a high mortality rate and poor prognosis. Advanced

in recent years[3]. The development of esophageal cancer (EC) from early to advanced stages is accompanied by a high mortality rate and poor prognosis.

Responses to Science editor

Q1. Please indicate where Figure 1 is located in the main text.

Response: Thank you for raising this issue, it is our negligence not to make it clear in the manuscript. We have revised the manuscript accordingly. Please refer to lines 101 on page 6.

diseases has become a hot research topic. CAD is an advanced technology used to preprocess endoscopic images, extract image features, process data and obtain diagnostic results with the help of computer algorithms and graphics processing technology[10] (Figure 1).

Q2. I recommend that tables including the outlines and results of each study are inserted in order to help readers' understanding..

Response: Thank you for your valuable advice. We have added two tables in the manuscript.

Table 1 Application of artificial intelligence in endoscopic detection of Barrett's esophagus

Reference	Year	Target disease	Endoscopic modality	AI technology	Database	Outcomes
van der Sommen *et al*[23]	2016	Early neoplasia in BE	WLI	SVM	100 images	Per-image sensitivity 83%/specificity 83%; Per-patient sensitivity 86%/specificity: 87%
Maarten *et al*[24]	2021	BE	WLI/NBI	CNN	Train 494364 images/1247 images; test 183 images/157 videos	Images: accuracy 84%/sensitivity 88%/specificity 78%; Videos: accuracy 83%/sensitivity 85%/specificity 83%
de Groof *et al*[25]	2020	Early neoplasia in BE	WLI	ResNet-UNet	Train 1544 images; test 160 images	Dataset 4: accuracy 89%/sensitivity 90%/specificity 88%; Dataset 5: accuracy 88%/sensitivity 93%/specificity 83%
de Groof *et al*[26]	2020	Barrett's neoplasia	WLI	ResNet-UNet	Train 1544 images; test 20 patients	Accuracy 90%/sensitivity 91%/specificity 89%
Hong *et al*[27]	2017	BE	Endomicroscopy	CNN	Train 236 images; test 26 images	Accuracy 80.77%
Hashimoto *et al*[28]	2020	Early neoplasia in BE	WLI/NBI	CNN	Train 1832 images; test 458 images	Accuracy 95.4%/sensitivity 96.4%/ specificity 94.2%
de Groof *et al*[29]	2019	Barrett's neoplasia	WLI	SVM	60 images	Accuracy 92%/sensitivity 95%/specificity 85%

BE: Barrett's esophagus; WLI: white light imaging; SVM: support vector machine; NBI: narrow band imaging; CNN: convolutional neural network

Table 2 Application of artificial intelligence in endoscopic detection of early esophageal cancer

Reference	Year	Target disease	Endoscopic modality	AI technology	Database	Outcomes
Ebigbo *et al*[37]	2019	EAC	WLI/NBI	CNN	248 images	Augsburg database: sensitivity 97%/specificity 88% (WLI); sensitivity 94%/specificity 80%(NBI); MICCAI database: sensitivity 92%/specificity 100%
Ebigbo *et al*[38]	2020	EAC	WLI	CNN	Train 129 images; test 62 images	Accuracy 89.9%/sensitivity 83.7%/specificity 100%
Horie *et al*[39]	2019	EC	WLI/NBI	CNN	Train 8428 images; test 1118 images	Accuracy 98%/sensitivity 98%
Cai *et al*[40]	2019	ESCC	WLI	DNN	Train 2428 images; test 187 images	Accuracy 91.4%/sensitivity 97.8%/specificity 85.4%
Ohmori *et al*[41]	2020	ESCC	WLI/NBI/BLI	CNN	Train 22562 images; test 727 images	Non-ME: accuracy 81.0%/sensitivity 90%/specificity 76%(WLI); accuracy 77%/sensitivity 100%/specificity 63%(NBI/BLI); ME: accuracy 77%/sensitivity 98%/specificity 56%
Liu *et al*[42]	2020	EC	WLI	CNN	Train 1017 images; test 255 images	Accuracy 85.83%/sensitivity 94.23%/specificity 94.67%
Kumagai *et al*[43]	2019	ESCC	ECS	CNN	Train 4715 images; test 1520 images	Accuracy 90.9%/sensitivity 92.6%/specificity 89.3%

Guo *et al*[44]	2020	ESCC	NBI	CNN	Train 6473 images; test 6671 images and 80 videos	Images: sensitivity 98.04%/specificity 95.03%; Videos: Non-ME sensitivity 60.8%(per frame)/100%(per lesion); ME sensitivity 96.1%(per frame)/100%(per lesion)
Tokai *et al*[46]	2020	ESCC	WLI/NBI	CNN	Train 1751 images; test 291 images	Accuracy 80.9%/sensitivity 84.1%/specificity 73.3%
Nakagawa *et al*[47]	2019	ESCC	WLI/NBI	CNN	Train 14338 images; test 914 images	Accuracy 91%/sensitivity 90.1%/specificity 95.8%
Zhao *et al*[48]	2019	ESCC	NBI	Double-labeling FCN	1350 images	Lesion level: accuracy 89.2%; Pixel level: accuracy 93%
Everson *et al*[49]	2019	ESCC	NBI	CNN	7046 images	Accuracy 93.7%/sensitivity 89.3%/specificity 98%
Uema *et al*[50]	2021	ESCC	NBI	CNN	Train 1777 images; test 747 images	Accuracy 84.2%
Fukuda *et al*[51]	2020	ESCC	NBI/BLI	CNN	Train 28333 images; test 144 patients	Accuracy 63%/sensitivity 91%/specificities 51%(detection); accuracy 88%/sensitivity 86%/specificities 89%(characterization)
Shimamoto *et al*[52]	2020	ESCC	WLI/NBI/BLI	CNN	Train 23977 images; test 102 videos	Non-ME: accuracy 87%/sensitivity 50%/specificity 99%; ME: accuracy 89%/sensitivity 71%/specificity 95%
Waki *et al*[53]	2021	ESCC	WLI/NBI/BLI	CNN	Train 18797 images; test 100 videos	Sensitivity 85.7%/specificity 40%

EAC: esophageal adenocarcinoma; WLI: white light imaging; NBI: narrow band imaging; CNN: convolutional neural network; EC: esophageal cancer; ESCC: esophageal squamous cell carcinoma; DNN: deep neural network; BLI: blue laser imaging; ME: magnification endoscopy; ECS: endocytoscopic system; FCN: fully convolutional network