

Dear Editor,

We are deeply grateful for your prompt reply to our manuscript entitled "Development of artificial intelligence technology in the diagnosis, treatment, and prognosis of colorectal cancer". We sincerely appreciate the constructive comments by you and professional reviewers. Based on your suggestions, the manuscript has been carefully revised, and hopefully our modified version would meet with your requirements and be published in World Journal of Gastrointestinal Oncology.

All the changes to the text have been marked in red in the revised manuscript. The responses to the comments are listed below in blue. In addition, the manuscript has been thoroughly checked before submission.

Thank you very much for your kind consideration. If you have any questions or comments, please feel free to contact us.

Sincerely yours,

Jiannan Li

Dear Reviewers,

Thank you so much for your valuable comments to our manuscript entitled "Development of artificial intelligence technology in the diagnosis, treatment, and prognosis of colorectal cancer". Your comments are very valuable and helpful for the improvement of our paper. According to your kind suggestions, we have revised the whole manuscript. We hope that this updated version will meet with your approval and be qualified to be published in World Journal of Gastrointestinal Oncology. All the changes to the text have been marked in red. The response to your comments is listed as follows.

Sincerely yours,

Jiannan Li

Reviewer reports:

Response to Reviewer 1:

1. This is an exceptionally interesting review that will deepen our understanding of the contribution of artificial intelligence in colorectal cancer diagnosis, treatment, and prognosis. The manuscript is concise, well-written and structured, and the tables quickly grab the readers' attention. Based on recent literature, the authors have collected valuable information regarding the utility of artificial intelligence systems in improving colorectal cancer screening and early diagnosis. Interestingly, the study also focuses on AI-based novel applications for a more personalized and targeted approach in colorectal cancer patients.

Response: Thank you very much for your comments.

2. The authors should include in the advantages of robot-assisted surgery that the learning curve for robotic colorectal surgery appears to be shorter than that required for laparoscopic surgery.

Response: Thank you very much for your comments. Based on your suggestions, we have provided this information in the robot-assisted surgery paragraph. The added part is also listed here.

“Because of the precise recognition and detailed operation of robotic surgery, the learning curve of robotic colorectal surgery is shorter than that of laparoscopic surgery.”

3. In addition, competition could drive the price of robotic surgical systems down.

Response: Thank you very much for your comments. Based on your suggestions, we have provided this information in the robot-assisted surgery paragraph.

“However, as competition can decrease the price of robotic surgical systems, its promotion will be accelerated in the future.”

4. The authors should also include that more prospective studies with real-time use of AI models during colonoscopy will be necessary for further validation in the near future.

Response: Thank you very much for your comments. We have provided this information in Section 2.6. The added part is also listed here.

“By calculating the risk and difference of detecting polyps, adenomas and CRC, Barua I, *et al.* compared colonoscopy with AI and colonoscopy without AI. It was found that an AI-based polyp detection system in colonoscopy could increase the detection rate of nonprogressive small adenomas and polyps but could not increase the detection rate of progressive adenomas^[90]. Wang *et al.* developed the ENDOANGEL system and compared AI colonoscopy with colonoscopy without AI through random control experiments. The results showed that AI significantly improved the detection rate of adenoma in colonoscopy^[91]. Lui TKL *et al.* suggested that the DL AI model could detect adenomas missed in routine colonoscopy in the real-time examination. They believed that the combination of AI and auxiliary equipment could eliminate the risk of missing lesions in colonoscopy when the intestine was well prepared^[92].”

5. Finally, the "black box" problem in machine learning raises several concerns regarding the widespread use of this novel technology in clinical practice.

Response: Thank you very much for your comments. We have provided this information in the Discussion part.

“Meanwhile, the “black box” problem in ML raises several concerns clinically. ML can help read imaging and pathological pictures, recommend diagnosis and treatment options, and predict prognosis. However, due to the “black box” problem, the clinical application of AI tools progressed slowly. To further develop AI medicine, it is

necessary to improve the interpretability of ML algorithms. The small steps of biological interpretation and clinical experience in ML algorithm can gradually solve the “black box” problem.”

6. Overall, this is a high-quality review of in-depth and extensive research. Taking into consideration the points mentioned above, I recommend the publication of this article.

Response: Thank you very much for your comments.

Response to Reviewer 2:

1. Is there any Smartphone based app for early detection of Polyp?

Response: Following your advice, we have searched the Web of science and PubMed databases. We are very sorry that we can't find the relevant literature about Smartphone based app for early detection of polyp. However, we have also revised the manuscript based on your suggestion in Section 2.6 (ML of AI in endoscopic diagnosis). The added part is also listed here.

“Tian X, *et al.* believed that enhanced patient education (EPE) can be realized through visual aids, telephone, mobile and social media applications, multimedia education and other software. EPE was used to guide the intestinal preparation of patients with colonoscopy and improve the detection rate of polyps, adenomas and sessile serrated adenomas^[97].”

2. What are the legal aspects associated with use of AI in Colorectal Ca?

Response: Thank you very much for your comments. We have provided this information in the Discussion part. The added part is also listed here.

“Various countries have been trying to establish ethical, legal, and regulatory compliance standards for AI development. But there are many difficulties before fully accepting AI robots. First, patients’ trust and acceptance will become an important factor in developing AI robotic surgery. The “black box” that has been used in many non-surgical applications has little theoretical transparency. In the medical field, lack of transparency impairs the doctors and patients' trust and acceptance of AI. Second, the safety of AI robot surgery is still an important issue to be concerned. The development of AI robot surgery involves a series of security problems, such as patient

information protection, network security, robot autonomy, machine failure, etc. If the control of the AI robot is lost due to external factors such as network transmission delay and hacker attack, the immeasurable loss will happen. Third, the responsibility attribution of medical malpractice remains a problem. Given the limitations of AI robots, the issues of medical malpractice responsibility will lead to a debate about the gray area of law. The solution of this problem will boost AI development^[160].”

3. What lies in the future to increase the sensitivity and specificity to identify CRC at an early stage?

Response: Thank you very much for your suggestion. We have provided this information in Section 2 in red. The added part is also listed here.

“It is important to increase the sensitivity and specificity of early detection of CRC. First, massive endoscopic image datasets of early CRC should be set, with the early screening performed by colonoscopy and AI automatic recognition system. Second, early identification and timely warning for high-risk groups with family history can be realized through new media and smartphone software. Third, with many pathological images and optical maps, we can identify whether the cutting edge is negative after endoscopic intervention in real-time to adjust the treatment plan in time and avoid secondary surgery. Fourth, the government should establish a timely and effective national physical examination plan through AI to conduct early intervention and treatment for the high-risk population.”

Response to Science editor:

1. The authors have performed a narrative review of the use of artificial intelligence for the diagnosis, treatment and prognosis of colorectal cancer. The article is well written and is relevant given the increasing use of AI in medicine.

Response: Thank you very much for your comments.

2. There was a review published previously by Wang et al (Review Am J Cancer Res . 2020 Nov 1;10(11):3575-3598. eCollection 2020) that should be discussed.

Response: Thank you very much for your comments. We have provided this information in the Discussion part. The added parts are also listed here.

“The four main directions of future medical development are “personalization, precision, minimal invasion and remote”^[159].”

“The development of AI for CRC has gone through the following stages: first, understanding cancer at the molecular and cellular levels through DL; second, assisting in the diagnosis of CRC according to images and pathological specimens; third, clinical drug designing and screening; fourth, promoting the individualization of CRC diagnosis and treatment^[159].”

3. It lacks information on the strategy used to identify relevant articles.

Response: Thank you very much for your comments. We have added the retrieval information of indexed literature in the Introduction part. The added part is also listed here.

“Web of Science and PubMed databases were used, keywords “artificial intelligence” and “colorectal cancer”.”

4. Refrain from the use of colloquial English terms in the abstract and body of text.

Response: Thank you very much for your comments. The language of this manuscript has been improved. We have checked and revised the language. In addition, this review has been polished by a professional company.

5. Please provide a methods section detailing your search strategy and terms used.

Response: Thank you very much for your comments. We have added the retrieval information of indexed literature in the Introduction part.

“Web of Science and PubMed databases were used, keywords “artificial intelligence” and “colorectal cancer”.”

6. The sections are informative but quite long, consider adding subheadings.

Response: Thank you very much for your comments. Based on your suggestions, we have added some subtitles in this review.

7. Table 1, consider adding the number of participants in the study and the control and interventions used.

Response: Thank you very much for your comments. We have revised the manuscript in table 1 based on your suggestions.

8. Further tables and/or Figures to help illustrate the major points in the text will be beneficial to readers.

Response: Thank you very much for your comments. We have made corresponding tables in sections 2, 3 and 4 to help readers better understand our article. Therefore, we don't add any new tables or figures.