Reply to Reviewers

Dear Editor and Reviewers:

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "**Esophageal cancer screening, early detection and treatment: current insights and future directions**" (**Manuscript number: 90987**). These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied comments carefully and have made corrections which we hope meet with approval. We used track changes mode to revise part of the manuscript. We have revised and resubmitted the revised manuscript. The main corrections in the paper and the responses to the reviewer's comments are as follows:

Responds to the reviewer's comments:

Reviewer #1:

The authors review the screening programs for esophageal cancer in the world, the importance of early detection and treatment, undelighting the insights and needs. The manuscript is well strctured. I have only few suggestion: A materials and methods section is lacking Geographical variations in e.c. screening paragraph is very interesting. I think that a figure or table to summarize could be useful A summary of pros and cons of diagnostic and therapeutic protocols could be useful for the reader.

Author response and action taken: Thank you for your valuable suggestion. Based on your suggestion, we have added t tables in order to present "The geographical variations of esophageal cancer screening" and "The pros and cons of diagnostic and therapeutic protocols in esophageal carcinoma" more clearly.

Table1. Geographical Variations in Esophageal Cancer Screening

Country	Governmental/Healthcare Policies	Definition of high-risk groups	Screening Strategies
China	China guideline for the screening, early detection and early treatment of esophageal cancer (2022, Beijing)[26]	(1) age ≥40 years from areas with high prevalence of esophageal tumors; (2) family history of esophageal tumors; (3) risk factors for esophageal cancer (smoking, heavy alcohol consumption, squamous carcinoma of the head and neck or respiratory tract, preference for high-temperature and preserved foods, poor oral hygiene, etc.)	Endoscopic screening: (1) High-risk groups: endoscopic screening with iodine staining of the esophageal mucosa is recommended (45 years⩽Age⩽75 years, Every 5 years). (2) Low-grade intraepithelial neoplasia every 1-3 years. (3) Low-grade intraepithelial neoplasia combined with endoscopic risk factors or lesions >1 cm in length will undergo endoscopy once a year for 5 years. (4) Endoscopy is recommended every 3 to 5 years for patients with Barrett's esophagus without atypical hyperplasia. (5) Endoscopy is recommended every 1 to 3 years for Barrett's esophagus patients with low-grade intraepithelial neoplasia. (6) A new type of esophageal cell collector is recommended for Barrett esophageal screening. (7) The new esophageal cell collector (Cytosponge) performs cytological examination combined with biomarker detection for effective primary screening of Barrett's esophagus-related dysplasia and early esophageal adenocarcinoma. (8) Biomarker testing alone not recommended for esophageal cancer screening. Equipment: Lugol color endoscopy or narrow band imaging (NBI) endoscopy is recommended as the first choice for esophageal cancer

			screening, ordinary white light endoscopy can be chosen for those with insufficient conditions, and magnifying endoscopy can be used in conjunction with NBI endoscopy for those with conditions.
American	ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus[21].	(1) male; (2) more than 5 years or frequent (at least once per week) symptoms of gastroesophageal reflux disease; (3) ≥2 risk factors for Barrett's esophagus or esophageal adenocarcinoma, risk factors including age >50 years, Caucasian ethnicity, centripetal obesity (waist circumference >102 cm or waist-to-hip ratio >0.9), history of smoking, and history of first-degree relatives with Barrett's esophagus or esophageal adenocarcinoma.	(1) Unsedated transnasal endoscopy (uTNE) can be considered as an alternative to conventional upper endoscopy for BE screening. (2) For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3 to 5 years. (3) Use of additional biomarkers for risk stratifi cation of patients with BE is currently not recommended. Equipment: Surveillance should be performed with high-definition/high-resolution white light endoscopy.
UK	British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus [18]	(1) white male; (2) age >50 years; (3) obese; (4) chronic GERD symptoms for more than 3 years; (5) first-degree relative with history of Barrett's esophagus or esophageal adenocarcinoma	(1) Endoscopic screening can be considered in patients with chronic GORD symptoms and multiple risk factors (at least three of age 50 years or older, white race, male sex, obesity). However, the threshold of multiple risk factors should be lowered in the presence of family history including at least one first-degree relative with Barrett's or OAC. (2) High-resolution endoscopy should be used in Barrett's oesophagus surveillance.

	years;	(3) Patients with Barrett's oesophagus shorter than 3 cm, with IM, should receive endoscopic surveillance every 3–5 years. (4) Patients with segments of 3 cm or longer should receive surveillance every 2–3 years. (5) Biomarker panels cannot yet be recommended as routine of screening.

Table 2. The pros and cons of diagnostic and therapeutic protocols in esophageal carcinoma

Treatment method	Indications	Pros	Cons
(1) For patients with early-stage EC who meet the absolute and relative indications for endoscopic resection, ESD being the first choice; (2) when the long diameter of the lesion is ≤10 mm, if the whole piece can be guaranteed resection, EMR treatment can also be considered. (3) For patients with early-stage EAC after EMR resection, ablation treatment is recommended. (4) Endoscopic radiofrequency ablation (RFA) can be used to treat ESCC limited to the lamina propria of the mucosa.	(1) The absolute indication of endoscopic resection of EC is that the lesion is limited to the epithelial layer and lamina propria of T1a esophageal cancer, and the risk of lymph node metastasis is low. (2) The relative indications of endoscopic resection: the lesion extends to the muscularis mucosa or slightly infiltrates the submucosa (the depth of submucosal infiltration is less than 200 μ m), the range is ⩾ 3/4 of esophageal circumference, and the	(1) EMR: Easy to operate and less invasive. Short operation time, low risk and quick recovery. (2) ESD: Larger tumors, especially those larger than 2 cm in diameter, can be completely removed at once, reducing the likelihood of recurrence. (3) RFA has a relatively short recovery time and demonstrates a low recurrence rate. (4) Surgery: completely remove the tumor, thereby reducing the risk of recurrence, and providing exact pathological staging information, which helps to assess the progression	(1) EMR: Difficulty in removing large or poorly defined tumors at one time, which may require multiple treatments and a relatively high rate of recurrence. (2) Technically demanding, the procedure takes longer and may increase the risk of complications, such as bleeding or perforation. (3) RFA: Narrow range of indications; may increase risks and complications, include pain, bleeding, esophageal stricture or perforation, requiring specialized equipment and trained physicians. (4) Surgery: there are risks associated with the surgery itself (e.g., infection, bleeding, anesthesia complications, etc.), possible postoperative complications (e.g., esophageal stricture, dysphagia,

(5) For patients with lesions infiltrating to a depth of submucosal (>200 μm) T1b stage EC patients with lymph node or vascular invasion and tumor low differentiation (≥G3), esophagectomy should be performed. Those who refuse surgery or are intolerant to surgery should be treated with concurrent radiotherapy and chemotherapy (CRT) [26].	risk of stenosis after resection is high. However, patients should be fully informed of postoperative stenosis and other risks. (3) Lesions with infiltration depths (>200 μm) up to the submucosal layer (T1b) are associated with metastasis, in which case they should be treated in the same way as advanced cancers, even if they are classified as superficial[26, 55].	of the cancer and plan subsequent treatment. (5) CRT: providing good local lesion control and helping to reduce tumor size, which may make surgery easier or, in some cases, avoid it; being effective in reducing the rate of tumor recurrence for some patients; and making CRT an effective treatment option for patients who can't afford to have surgery due to health issues.	malnutrition, etc.), and negative impact on the patient's quality of life, especially in terms of digestive function and eating habits. In addition, the long postoperative recovery time may require additional nutritional support and rehabilitation. (5) CRT: include a wide range of possible side effects from chemotherapy and radiation (e.g., nausea, vomiting, hair loss, fatigue, loss of appetite, etc.); the potential for a long-term decline in quality of life, such as digestive problems and difficulty swallowing; and the potential for a wide-ranging impact on a patient's overall health status, especially for patients who are older or who have other health problems.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. Here we did not list all the changes but marked in yellow in the revised paper.

We appreciate for Editors/Reviewers' work earnestly, and hope that the correction will meet with approval. We are open to any additional comments or concerns you may have regarding this adjustment or any other aspect of the paper. Your feedback is invaluable in improving the quality of our work. Thank you for your support.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Fang Zhang