

Point-by-point responses to the issues raised in the peer-review report(s) for manuscript 86319:

Reviewer #1:

I think that the predictive factors put forward by the authors will be a guide for prospective studies. However, many predictive factors need to be confirmed by new studies. **However, I think that a rigorous and detailed conclusion section will contribute to the literature.**

Dear reviewer, thanks a lot for your kind suggestion. Here we rewrote the conclusion as “Various factors, including preoperative imaging, serum markers, preoperative pathology and immunohistochemical indicators, were predictive of lymph node metastasis in early ESCC and EAC. Several comprehensive models predicting lymph node metastasis in early ESCC performed well, but these models relied on postoperative pathology. Further studies focusing on serum markers, imaging and immunohistochemical indicators are still needed.”

Reviewer #2:

The authors reviewed the predictive factors for lymph node metastasis in early esophageal cancer. This review article is a good summary of the current evidence, especially for the molecular findings, and is of high value. **Unfortunately, there is a fundamental misunderstanding that needs to be corrected.**

1. Lymph node metastasis is important in determining the therapeutic strategy for early esophageal cancer. This is not the first review of this topic; countless reviews have been written since the 20th century, and the relationship between depth of invasion and rate of metastasis is already common knowledge to most researchers.

Dear reviewer, thanks a lot for your kind suggestion. This study aimed to review all indicators that could predict lymph node metastasis in early esophageal cancer. Here we added “Indicators that could be used to predict

lymph node metastasis in early esophageal cancer have been reported in many recent studies, but no recent studies have included a review of this subject” in the “Background” section and “Indicators that could be used to predict lymph node metastasis in early esophageal cancer have been reported in many recent studies, but no recent studies have included a review of this subject” in the “Introduction” section. Moreover, we added “reflecting common knowledge to most researchers” in the paragraph about submucosal invasion in the “Postoperative Pathology and Immunohistochemical Analysis” section.

2. Lymph node metastasis of early-stage esophageal cancer highly depends on the depth of invasion. Diagnosis of the depth of invasion of esophageal cancer has progressed dramatically over the past 20 years with the advent of NBI and magnifying endoscopy. Without such information, it would be inadequate to speculate about lymph node metastasis.

Dear reviewer, thanks a lot for your kind suggestion. Here we added “Preoperative narrow band imaging and magnifying endoscopy contributed to the assessment of the invasion depth of early esophageal cancer” in the paragraph about submucosal invasion in the “Postoperative Pathology and Immunohistochemical Analysis” section.

3. Lymph node metastasis of early esophageal cancer highly depends on the depth of invasion. The mortality after surgery for esophageal cancer cannot be ignored, so since the 20th century, a treatment strategy has been adopted: esophageal cancer with a preoperative diagnosis up to SM1 should first be resected by ESD, and the decision of subsequent surgery is examined by the depth of invasion and vascular invasion. Therefore, there is no clinical problem using the information obtained from ESD specimens to predict lymph node metastasis. This paper lacks the perspective of the actual treatment strategy.

Dear reviewer, thanks a lot for your kind suggestion. Here we added “This therapeutic strategy has been widely adopted: esophageal cancer with a

preoperative diagnosis of invasion into SM1 is first resected endoscopically, and the decision regarding subsequent surgery is informed by the depth of invasion and vascular invasion” in the paragraph about submucosal invasion in the “Postoperative Pathology and Immunohistochemical Analysis” section. Moreover, we added “In this study, we reviewed predictive indicators of lymph node metastasis in patients with early esophageal cancer, especially as observed in recent findings about serum markers, immunohistochemical indicators and comprehensive models” and “The present therapeutic strategy involves suggested initial endoscopic resection before subsequent surgery based on the depth of invasion and vascular invasion in patients with a preoperative diagnosis of SM1 invasion” in the “Discussion” section.

4. The rate of lymph node metastasis of esophageal adenocarcinoma varies depending on the location and the metastatic site. This needs to be considered.

Dear reviewer, thanks a lot for your kind suggestion. We know ESCC and EAC differed a lot in tumor location and biological behavior. But we didn’t find that tumor location and the metastatic site were related to the rate of lymph node metastasis of esophageal adenocarcinoma. We added “ESCC mainly occurs in the proximal two-thirds of the esophagus, while EAC mainly occurs in the distal third of the esophagus and the gastroesophageal junction. Alcohol and tobacco are risk factors for ESCC, and Barrett’s esophagus is correlated with EAC” in the “Introduction” section.