Peer Review File

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Reviewer A

Pathologically, Mucinous and Adenocarcinoma differ histologically, but clinically, the results do not change. This is an interesting paper, and I have a few points I would like to confirm:

1. How many cases of Mucinous and Adenocarcinoma underwent neoadjuvant therapy? Additionally, what is the ratio of RT (Radiotherapy) to Chemotherapy?
2. What is the diagnostic rate of Mucinous preoperatively?
3. What is the pathological therapeutic effect evaluation in cases where neoadjuvant therapy was administered?

#Comment 1: How many cases of Mucinous and Adenocarcinoma underwent neoadjuvant therapy? Additionally, what is the ratio of RT (Radiotherapy) to Chemotherapy?

Reply 1: We thank the reviewer for bringing this to our attention. We did not include neoadjuvant therapy in our analysis. The proportion of patients with mucinous and adenocarcinoma receiving radiotherapy was 54.3%, and the proportion of chemotherapy was 63.5%.

Change in the text: None

#Comment 2. What is the diagnostic rate of Mucinous preoperatively?

Reply 2: We examined the data set obtained from the SEER database, and by screening the "Diagnostic Confirmation" field in the data set, we learned that nearly all patients with MAC had a diagnosis of mucinous carcinoma that was confirmed by means of preoperative biopsy or exfoliative cytology.

Change in the text: None

#Comment 3: What is the pathological therapeutic effect evaluation in cases where neoadjuvant therapy was administered?

Reply 3: In cases receiving neoadjuvant therapy, pathological response assessment typically involves looking at tumor shrinkage or pathological response to neoadjuvant therapy.

Change in the text: None

Reviewer B

According to author's data, there is no difference about prognosis among mucin-producing adenocarcinoma (MA), Esophageal cancer with signet-ring cell and conventional ADC.

Esophageal cancer with signet-ring cell features is associated with poor prognosis in the modern treatment era: factors influencing overall and disease-free ... HER2 expression in esophageal cancer with signet-ring cell features appears to portend a particularly poor prognosis.

Mucin-producing adenocarcinoma (MA) exhibits a more advanced clinical presentation and worse prognosis than conventional adeno-carcinoma (CA) in patients undergoing esophagectomy.

How about above data?

Please tell me the etiology about mucin-producing adenocarcinoma (MA).

#Comment 1: According to author's data, there is no difference about prognosis among mucin-producing adenocarcinoma (MA), Esophageal cancer with signet-ring cell and conventional ADC.

Reply 1: We sincerely thank the reviewer for careful reading. Our findings suggest that there were no significant differences in the characteristics of the three groups of patients and that esophageal MAC may be as malignant as esophageal SRC and AC. Therefore, esophageal MAC may not need to be distinguished from AC and SRC, which is in line with the World Health Organization Classification of Tumors of the Digestive System (5th edition, 2019), which no longer recommends classification of esophageal MAC as a separate subtype. In our opinion, this point highlights an important direction when dealing with these cancers in clinical practice, i.e. it may not be necessary to differentiate between these subtypes in treatment decisions. This could simplify treatment options and standardize prognostic assessment criteria, thereby contributing to improved patient management. We believe that further studies should explore the potential differences between these subtypes at the molecular and genetic levels to validate the applicability of current classifications and potentially guide future treatment strategies.

Change in the text: None

#Comment 2: Esophageal cancer with signet-ring cell features is associated with poor prognosis in the modern treatment era: factors influencing overall and disease-free ... HER2 expression in esophageal cancer with signet-ring cell features appears to portend a particularly poor prognosis. Mucin-producing adenocarcinoma (MA) exhibits a more advanced clinical presentation and worse prognosis than conventional adeno-carcinoma (CA) in patients undergoing esophagectomy.

How about above data?

Reply 2: Cancers characterized by signet ring cells and mucus-producing adenocarcinomas (MA) have a poor prognosis in contemporary therapeutic species. In particular, esophageal cancers with HER-2 expression have a particularly poor prognosis, probably because overexpression of HER2 leads to more aggressive cancer cells that are more resistant to treatment. On the other hand, MA shows more severe clinical manifestations and poorer prognosis in patients undergoing esophagectomy compared to conventional esophageal adenocarcinoma, possibly because MA is often diagnosed at a more advanced stage and its biology may promote a more aggressive local tumor microenvironment that promotes resistance to conventional therapies. Cancers detected at an advanced stage usually require more aggressive treatment approaches, including surgery, radiotherapy and chemotherapy. Therefore, we need to emphasize improved diagnostic and therapeutic strategies to improve patient outcomes and prognosis.

Change in the text: None

#Comment 3: Please tell me the etiology about mucin-producing adenocarcinoma (MA).

Reply 3: Causes of Mucinous Adenocarcinoma: Mucus-producing adenocarcinomas (MA) among esophageal cancers usually present with more severe manifestations and have a poorer prognosis than esophageal adenocarcinomas (CA). MA originates from cells originating from the esophageal epithelium that undergo malignant transformation and are capable of secreting mucus in large quantities.

Factors affecting the development of MA include mutations in genes such as the Kirsten rat sarcoma viral oncogene homolog (KRAS) and epidermal growth factor receptor (EGFR) that affect cell signaling pathways that regulate cell proliferation and survival, leading to MA; in addition, chronic irritation caused by tobacco smoking and dietary factors, and long-term chronic In addition, chronic irritation and long-term chronic inflammation caused by smoking and dietary factors can lead to alterations and malignant changes in esophageal cells, thus promoting the development of MA. These factors may lead to a more advanced stage of MA at the time of diagnosis and a poorer response to treatment, thus affecting prognosis.

Change in the text: None

Reviewer C

#Comment 1: It is unclear what the histological relationship is between MAC, SRC and AC.

On page 2, line 39, author describes AC as being a mixed histological type of MAC and SRC. However, the percentage of MAC and SRC in AC is not presented, and it should be indicated how much MAC and SRC are included in the AC group. This is a critical shortcoming of this paper.

Reply 1: Thanks for your kind reminder. We reviewed the literature again and only a subset of adenocarcinomas has a mixed histologic pattern, including imprinted cell and mucinous histology, so we modified the content in the Introduction section. We have listed the number of patients in each of the three types in the results section, and we will add their percentages. (see Page 3, line 71-73; page 4 line 135- page5, line 136)

Change in the text: Esophageal cancer is a common gastrointestinal cancer with 604,100 new cases and 544,076 deaths worldwide according to 2022 global cancer statistics [1]. The two main histopathological types of esophageal cancer are squamous cell carcinoma and adenocarcinoma (AC)[2]. Signet-ring cell carcinoma (SRC) is characterized by large intracellular mucin aggregates and compressed nuclei displaced toward one end of the cell, while mucinous adenocarcinoma (MAC) has abundant extracellular mucin [3].

A total of 497 patients (2.2%) with MAC, 21109 patients (92.8%) with AC and 1144 patients (5%) with SRC were included in the study.

#Comment 2: The author states that the independent factors of OS and CSS in MAC are T, N, M, and surgery, which is not limited to MAC but is obvious in many cancers. He also recommends early surgery, which is also not surprising.

Reply 2: Thank you for pointing this out. Indeed, we found that the independent influences (T, N, M and surgery) affecting MAC OS and CSS are important clinical parameters common to many types of cancers, and the reason why these factors are prevalent in many types of cancer tumors is that they do have a significant impact on cancer prognosis and treatment decisions, and although the privacy of these influences is prevalent, the specific prognostic impact of these factors may vary in different types of cancer tumors. influence may vary in degree and manner. The concentration factors identified in our study can be explored and analyzed in different ways in subsequent studies. For example, interactions with other biomarkers or treatment modalities could be investigated. We believe that even these few common influencing factors could reveal new, meaningful information in specific subsequent studies to help improve treatment strategies and prognostic assessment.

Change in the text: None

#Comment 3: It is unclear for what purpose the authors created the nomogram. A nomogram including MAC, AC, and SRC would be more significant than a nomogram of MAC alone, since there is no difference in prognosis.
Reply 3: We thank the reviewer for bringing this to our attention. As our study was mainly focused on esophageal MAC analysis, so we are only using multivariate Cox regression model analysis of MAC, OS and CSS to predict survival in patients with nomogram model.
Change in the text: None

#Comment 4: The abbreviation "SEER" on page 1, line 6 is a first mention, but the abbreviation is not defined.
Reply 4: We sincerely thank the reviewer for careful reading. We have modified our text as advised. (see Page 2, line 35)
Change in the text:
The Surveillance, Epidemiology, and End Results database (SEER) database was used to compare the clinical characteristics and prognosis of patients with esophageal mucinous adenocarcinoma (MAC), esophageal adenocarcinoma (AC) and esophageal signet-ring cell carcinoma (SRC) and to develop nomograms.

#Comment 5: A typical histological picture of the MAC, AC, and SRC should be presented.
Reply 5: We thank the reviewer for bringing this to our attention. Unfortunately, the data used in our study were all obtained from the SEER database; MAC is a rare disease in our country and we have difficulty in obtaining copyrighted histological images.
Change in the text: None

#Comment 6: Tumor localization should also include the Esophago-Gastric junction.
Reply 6: Thanks for your kind reminder. In the SEER database, data on the location of esophageal cancer are only included: C15.0-Cervical esophagus; C15.1-Thoracic esophagus; C15.2-Abdominal esophagus; C15.3-Upper third of esophagus; C15.4-Middle third of esophagus; C15.5-Lower third of esophagus; C15.8-Overlapping lesion of esophagus; C15.9-Esophagus, NOS.
Change in the text: None

#Comment 7: The covariates used in the multivariate analysis should be clearly indicated.
Reply 7: Thanks for your kind reminder. We have modified our text as advised. (see Page 5, line 176-178)
Change in the text: Univariate and multivariate Cox analyses were performed to identify significant prognostic factors **(Tables 2 and 3)**. For patients with MAC, according to univariate Cox analysis, age, T stage, N stage, M stage, AJCC stage, and surgery were significantly related to OS,

and these factors were included in the multivariate COX analysis. Sex, T stage, N stage, M stage, AJCC stage, and surgery were significantly associated with CSS, and these factors were also included in the multivariate COX analysis. N stage, M stage, and surgery were found to be independent prognostic factors for both OS and CSS by multivariate Cox analysis ($P < 0.05$). For OS, T stage was also an independent prognostic factor (HR, 1.417, 95% CI: 1.005-1.999, $P = 0.047$).