Peer Review File

Reviewer Comments

Comment 1: The title should indicate the nature of a narrative survey/review for the readers. As the authors explain the role of non-coding RNA in the context of diagnosis, treatment and prognosis throughout of the manuscript, the authors should this aspect in the title, too.

Reply 1: Thanks for your comments on the title. We have modified our text as advised (see Page1, line1-3)

Changes in the text: Page 1, line 1-3.

Comment 2: The background section is too long and must be shortened. Furthermore, the abstract misses a definitive result section. Please add.

Reply 2: The background section in the abstract is a bit general, so it has been refined (see Page, line 21-36), sorry for missing the result section, has been added(see Page 1,line 42-44),and we have improved the discussion section, please advise(see Page 2,line 47)

Changes in the text: Page, line21-36, line42-44 and Page 2, line 47

Comment 3: Please specify the histological subtypes of esophageal cancer for better understanding in this section and throughout the manuscript.

Reply3: Sincerely thank you for your suggestions for explaining the histology of esophageal cancer so that readers can clearly understand the article，we do ignore the introduction to the pathological types of esophageal cancer，we added，and when molecular biomarkers are used to diagnose early esophageal cancer, it is impossible to know its histological type in advance. Therefore, when writing the manuscript, it is first to perform non-coding RNA and Search the literature related to esophageal cancer, and there are certain descriptions in the discussion and table section. We detail the type of marker application in the table (see Page 2, line 56-57，table 3-5)

For example, the histopathological classification of esophageal cancer is different, and the markers used will be different, so we choose not to specify a type to describe, but if there is an opportunity, we can clarify the tissue type in future studies or reviews

Changes in the text: Page 2, line 56-57 and table3-5

Comment 4: Please specify in detail, how many hits with the applied online query algorithm happens. Furthermore, the inclusion and exclusion rate should be specified. Finally, the kind of publication (in-vitro, in-vivo and in-situ should) should be specified, too. These missing data could be presented in a separate figure.

Reply 4: Thanks for noting the loss of the above data，we added a figure and the retrieval type, article filtering rules in detail(see Page 5, line 113-122，Figure 3)

Changes in the text: Page 5, line 113-122，Figure 3

Comment 5: What are esophageal trawl cells? Please explain or show an example.

Reply 5: Sorry for not explaining the early professional approach and leaving readers wondering. About esophageal trawl cells，we have modified our text as advised (see Page 6, line 141-145)，We asked professional doctors and consulted relevant literature on a professional interpretation of this approach

Detailed technical introduction: a deflated balloon covered by a cotton or silk net is swallowed into the stomach, inflated, and then withdrawn, collecting exfoliated cells and scraping the surface of the esophageal mucosa. At the upper esophageal sphincter, the balloon is deflated and removed, and the attached cells are smeared directly onto glass slides. The spiders are then fixed in ethyl alcohol, stained with Papanicolaou's stain, and read for evidence of cellular abnormalities.

Changes in the text: Page 6, line 141-145

Comment 6: Please exchange "skill and experience of surgeons" with "skill and experience of pathologists and surgeons".

Reply 6: we have modified our text as advised (see Page 6, line 159)

Changes in the text: Page 6, line 159

Comment 7: According to the sentence "Along with the continuous renewal … further development and progress." give a new figure for the algorithm of therapy for local, extended and advanced esophageal cancer.

Reply 7: yes，thank you for your suggestion, it will allow readers to better understand，we add some data in new table1 （see Page 6, line 138-139，Table 1）

Changes in the text: Page 6, line 138-139，Table 1

Comment 8: Please correlate the absolute number of cases with esophageal cancer to the density of each population. Please add data for Europe. Please specify the year-dependent data for China, too

Reply 8: Thank you for the lack of data in this manuscript, we added some data and figure (see Page 2, line 61-81，Figure1)

Changes in the text: Page 2, line 61-81，Figure1

Comment 9: Section "Previous studies on the genomics of esophageal cancer" is rather superficial and should avoid common platitudes like "metastatic, and the latter depends on gene mutation".

Reply 9: we have modified our text as advised （see Page 9, line 208-224）

Changes in the text: Page 9, line 208-224

Comment 10: Figure1: Please correlate the absolute number of cases with esophageal cancer to the density of each population. Please add data for Europe. Please specify the year-dependent data for China, too

Reply 10: Thank you for the lack of data in this manuscript, we added some data and figure (see Page 2, line 61-81，Figure1)

Changes in the text: Page 2, line 61-81，Figure1

Comment 11: Table 1, 2 and 3: Please add rows to indicate the specific study setting of the findings (in-vitro, in-vivo and in-situ). Furthermore, please separate the common

Reply 11: Thank you for the lack of data in this manuscript，we have modified our text as advised（see Page 15, line 331-335，Page 17, line 398-406，Page 20, line 487-493 and Table 3, 4 and 5）

Changes in the text: Page 15, line 331-335，Page 17, line 398-406，Page 20, line 487-493 and Table 3, 4 and 5

Comment 12: The authors should specify how the best marker profile of non-coding RNA could be developed and evaluated in the future

Reply 12: Hello, thank you for your comments. We have added relevant information to the discussion and summary sections of the manuscript(see Page 10, line 257-274，Page 21, line　512-515 and Table 2)

Changes in the text: Page 10, line 257-274，Page 21, line　512-515 and Table 2

Comment 13: Please discuss and integrate following literature:

Reply 13: Thank you for recommending excellent literature related to the topic. This cell literature is very worthy of in-depth study. I have learned a lot from many knowledge points. The manuscript of this film discusses and integrates according to my shallow understanding of this article. Hope that experts will provide guidance.

Comment 14: Please check the manuscript for typos like ", Genomics" or "the Epithelial-mesenchymal transition"

Reply 14: Thank you for pointing out the spelling mistakes. I have searched professional vocabulary and corrected the spelling mistakes.

Changes in the text: The manuscript

Comment 15: What is the motivation of this work? The authors should clearly describe what is the difference between these papers and the current review.

Reply 15: The topic of this review is that we are currently working on related topics and have collected hundreds of esophageal cancer-related cases. Therefore, this review is written to understand the current research dynamics and do background investigations for subsequent data analysis. Next, write this review. The purpose is also to provide other researchers with relevant latest research, such as the stage of development of the newly found non-coding RNA biomarkers, which pathways may be related to them, finding the relevant expressed protein, whether it has been verified by in vivo experiments, etc.

Different from other research articles, the experimental results and conclusions can be seen directly and concisely from this review, and the desired information can be found; different from other review articles, more comprehensive and updated information can be seen from this review. In related research, the articles used this time are all recent articles with high references.

Changes in the text: NONE

Reply 16: yes，the methods for the detection of non-coding RNA biomarkers for early diagnosis of esophageal cancer do need to be fully explained, we added some data and figure (see Page10 , line 257-264，Figure4)
Changes in the text:Page10 , line 257-264，Figure4

Reply 17:we have modified our text as advised(see Page11 , line 269-274，Table 2)
Changes in the text:Page11 , line 269-274，Table 2

Reply 18: we added some data to summarise the major advantages and disadvantages of these methods (see Page 11, line 264-269, Table 2)
Changes in the text: Page 11, line 264-269, Table 2

Reply 19: we have modified our text as advised (see Page 20, line 501-526)
Changes in the text: Page 20, line 501-526