Response letter

(Changes are highlighted in red color in the marked version of the manuscript)

Reviewer's code: 02741591

SPECIFIC COMMENTS TO AUTHORS

Illustrative figures are encouraged and a better structure of the subheadings is warranted. It is unusual to include references in the conclusion. The tables are too long and should be better wrapped up.

Response: Thanks for your comment. First of all, we drew an illustrative figure to show graphical representation of sensitivity versus specificity of autoantibodies in ESCC that were evaluated in more than one study. We added the content about this figure in the revised manuscript (Page 9), which now reads "The graphical representation of the sensitivities and specificities for autoantibodies in ESCC evaluated in more than one study is shown in Figure 1.". Moreover, we restructured the subheadings, and there were 7 subheadings in the revised manuscript. For the references in the conclusion section, we have deleted them in the revised manuscript. On the other hand, since we try to do our best to present all the autoantibodies evaluated in ESCC and EGJA in this review manuscript, it is hard to avoid long tables.

Reviewer's code: 02540539

SPECIFIC COMMENTS TO AUTHORS

This review revealed that tumor associated autoantibodies have high specificity and not so high sensitivity. Combined use is effective for improving sensitivity. This manuscript deserves publication.

Response: We are very grateful for your comments on the manuscript.

Reviewer's code: 03293239

SPECIFIC COMMENTS TO AUTHORS

Please provide in a table a brief summary of the biological significance of the major predictive tumor associated antibodies.

Response: Thanks for your good suggestion. In the revised manuscript, we added a table (see the Table 1 below) to briefly summarize the biological significance of several common tumor-associated autoantibodies. Specially, a sentence about this table was added in the revised manuscript (Page 6), which now reads "Moreover, autoantibodies are also reported as biomarkers used in cancer prognosis and therapeutic monitoring (Table 1)".

Table 1. A brief summary of the biological significance of some common tumor-associated autoantibodies

Representative tumor-associated autoantigens	Authors, year [Ref]	Tumor type	Biological significance
p53	Chapman et al, 2012[11]	Lung	Early detection
	Takeda et al, 2001[14]	Colorectal	Increased recurrence
	Anderson et al, 2010[15]	Ovarian	Increased survival
NY-ESO-1	Shan et al, 2013[16]	Lung	Early detection
	Fosså et al, 2004[17]	Prostate	Decreased survival
	Elke et al, 1999[18]	Melanoma	Therapeutic monitoring
MUC1	Pedersen et al, 2014[19]	Ovarian	Early detection
	Kurtenkov et al, 2007[20]	Gastric	Increased survival
Hu	Chapman et al, 2011[11]	Lung	Early detection
	Graus et al, 1997[21]	Lung	Therapeutic monitoring and increased survival

Reviewer's code: 03476648

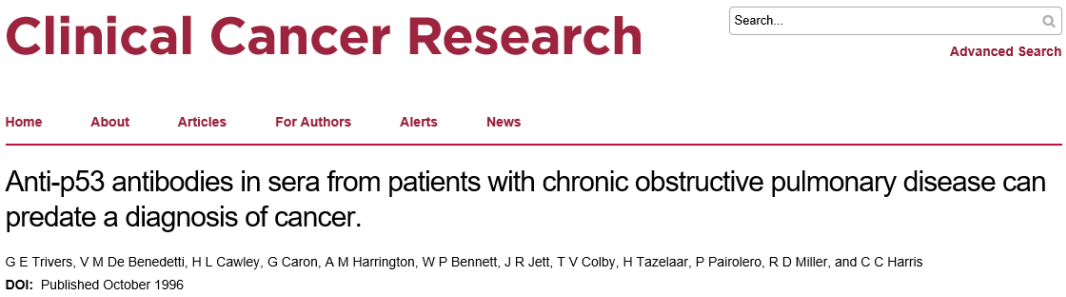
SPECIFIC COMMENTS TO AUTHORS

The present review article by Xu YW et al provides an interesting and comprehensive overview of the diagnostic potential of autoantibodies for the early detection of esophageal carcinoma. I have the following suggestions: (1) A brief presentation of the most promising biomarker approaches, other than autoantibodies, that have been suggested for the early detection (stage I) of esophageal cancer would be relevant to include. How do autoantibodies compare to such approaches? (2) Are there any successful examples of autoantibody application as diagnostic biomarkers for other cancers?

Response: According to the reviewer's good suggestions, in the CONCLUSION AND PERSPECTIVES part of the revised manuscript, we added the contents about other promising biomarkers for the early detection of esophageal cancer and a successful example of autoantibody application as diagnostic biomarkers for lung cancer, which now reads "In recent decades, a large number of blood-based cancer biomarkers, such as cell-free circulating tumor DNAs, various non-coding RNAs, proteins and TA autoantibodies, have been identified and indicate the potential for early detection of esophageal cancer. Among these biomarkers, TA autoantibodies are promising biomarker entities in the early cancer detection, as they are capable of identifying cancer in high-risk individuals. Moreover, they are highly stable and can be easily detected by routine method (e.g. ELISA). Recently, a TA autoantibody assay named *EarlyCDT*-Lung (against p53, NY-ESO-1, CAGE, GBU4-5, MAGE A4, SOX2 and Hu-D) approved by the FDA has been clinically and analytically validated."

Response to the editor's suggestions:

1. Running title have been revised as "Autoantibodies for ESCC and EGJA".
2. For the references 13, 23, 24 and 30, we tried our best to search the DOI numbers, but we really can't find them. For example, as shown below, the reference 13 is from a paper published in CCR in 1992, but no DOI could be obtained. Could you please help us to find them? Thank you.



3. The abbreviations in the title of the tables have been excluded and we explained all the abbreviations in the table legends.