

September 3, 2017

Subject: Response letter manuscript (No. 35154)

Dear editor and reviewers,

Thank you very much for reviewing our manuscript entitled *'The tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: a retrospective cohort study'* (35154), as well as for giving us the opportunity to improve the manuscript based on the valuable suggestions of the reviewers and resubmit. We deeply appreciate the comments and suggestions made by the reviewers that have considerably helped us to improve the scientific quality of the manuscript. Below, you will find our response (in blue) to each point brought up by the reviewers. In the revised manuscript (35154-Revised manuscript) all the additions/changes compared with the original manuscript are highlighted (in blue).

Yours sincerely,

The authors

COMMENTS

1. Page 1, title: *'The tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: a retrospective cohort study'*.

Comment: a succinct and impactful title will include minimal nonfunctional words, such as "a," "an," "the," "roles of," etc. and will avoid non-standard abbreviations. Please revise the title.

Response: We agree with the reviewer. We changed the title into: **'Tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: a retrospective cohort study'**

2. Page 4. Comment: Please offer the audio core tip.

Response: We have made an audio file describing the final core tip of the manuscript.

3. Page 12. Comment: Please write the comments. Writing requirements for each subsection

(1) Background

To summarize concisely and accurately the relevant background information so that readers may gain some basic knowledge about your study's relevance and understand its significance for the field as a whole.

(2) Research frontiers

To introduce briefly the current hotspots or important areas in the research field as related to your study.

(3) Innovations and breakthroughs

To summarize and emphasize the differences, particularly the advances, achievements, innovations and breakthroughs, as compared to other related or similar studies in the literature, which will allow the readers to assimilate the major points of your article.

(4) Applications

To summarize the practical applications of your research findings, so that readers may understand the perspectives by which this study will affect the field and future research.

(5) Terminology

To describe concisely and accurately any terms that may not be familiar to the majority of the readers, but which are essential for understanding your article.

Response: We have added this section to the manuscript.

4. Comments/suggestions reviewer 3:

1. What is the rational adopted to classify the TSR in the three categories proposed, and to choose those specific cut-off? It could be useful, according to

the results shown in Fig 3, to pool together patients classified as “low” and “intermediate” TSR, since they look to have super imposable survival profiles. I would prefer to see all the patients included in one of the two categories (good vs bad prognosis) according to TSR. I would test this classification (“high” vs “low/intermediate”) also in N0/ N+ subgroups of patients. Otherwise it is not clear what should be the prognostic meaning of having a “low” TSR.

Response: Thank you for your question.

The interobserver agreement for absolute scores was moderate. The correlation coefficient improved to good, when grouping as TSR-low, TSR-intermediate, and TSR-high. The categorization into these categories was performed with the aim of generating enhanced prognostic information based on the TSR, which had been executed earlier in a previous study on the TSR in oesophageal adenocarcinomas[17]. Other studies concerning the TSR used an arbitrary cut-off value of 50%. No differences in the given survival rates were found at this and other cut-off values in our population (see Appendix 1 of the manuscript).

2. Could the analysis be stratified by adjuvant treatment (yes vs no) and “high” vs “low/intermediate” TSR to see if this marker could be also used as predictive of adjuvant treatment outcome?

Response: This is an interesting suggestion. However, the adjuvant treatment outcome was not one of the scopes of the current study.