

Dear Editor:

Thank you for the opportunity to revise our manuscript “Adenosquamous carcinoma may have an inferior prognosis to signet ring cell carcinoma in patients with Stage I and Stage II gastric cancer”. Manuscript NO: 51148. Please skim our reply to the reviewers.

Please do not hesitate to contact me with any questions. E-mail: 347952582@qq.com

Yours sincerely,

Chu Yuxin, China.

To Reviewer #1:

(1) The title has been revised to “Adenosquamous carcinoma may have an inferior prognosis to signet ring cell carcinoma in patients with Stage I and Stage II gastric cancer”.

(2) All the abbreviations have been removed from the Abstract. According to your suggestion, the new sentence is “Totally 6063 patients with adenosquamous and signet ring cell gastric cancer were identified.” The conclusion has been revised accordingly.

(3) The importance of histology in gastric cancer has been added in our revised manuscript. Thanks for recommending 2 important references, we have revised our introduction accordingly to your recommendations. The inappropriate sentence and relevant reference have been removed accordingly.

(4) The SEER registries span from 1975 to 2015, so the length of years is 40. Preliminarily, 10646 patients with adenosquamous and signet ring cell gastric cancer were collected, but 4583 cases were excluded because of any missing data or unknown of table variables. Finally, a total of 6063 eligible patients were included in this study. We have obtained an exemption for this study from our Human Studies Subcommittee. Please skim our attachments.

(5) This sentence has been revised accordingly.

(6) Discussion:

Based on the cohort after PSM, our study has revealed the concrete CSS and OS of patients with SRC. The results after PSM have adjusted many confounders, so they may be more convincing. Moreover, our Cox proportional hazards regression models have identified radiotherapy and surgery as independent protective factors for improving their prognosis ($HR < 1$, $p < 0.05$). Hence our results may improve the therapeutic recommendations for these patients. Please skim our revised discussion in red lines.

In our univariate Cox regression analysis (**Table 4**), the HR of receiving radiotherapy is 0.484; 95%CI: 0.383-0.612, $p < 0.001$. In multivariate Cox regression analysis (**Table 4**), the HR of receiving radiotherapy is 0.587; 95%CI: 0.444-0.776, $p < 0.001$. Both $HR < 1$, $p < 0.001$, so radiotherapy was found to be an independent protective factor for patients' cancer specific survival. Hence our study has provided evidence to support radiotherapy for the patients.

This sentence means "The prognosis of ASC patients at stage I and stage II should be concerned".

(7) According to our study, we have found that ASC may have an inferior prognosis to SRC in patients with Stage I and Stage II gastric cancer, so greater attention should be paid to these patients. Histological type ASC and higher TNM stage were associated poor survival, but radiotherapy and surgery were independent protective factors for improving their prognosis. Our study supports radiotherapy and surgery for the future management of this clinically rare entity. The reasons for performing this study have been stated in our revised "Introduction".

To Reviewer #2:

1. The SEER database comprises 18 cancer registries and covers approximately 30% of the USA population, so it represents American rather than Chinese data.

2. Gastric signet ring cell carcinoma represents a unique histologic subtype of gastric adenocarcinoma, but the undifferentiated adenocarcinoma is confounded with many subtypes. Moreover, the comparison between adenosquamous carcinoma and gastric adenocarcinoma has already been published in "Feng F, Zheng G, Qi J, Xu G, Wang F, Wang Q, et al. Clinicopathological features and prognosis of gastric adenosquamous carcinoma. *Sci Rep*, 2017;7:4597". So our study focused on the comparison between ASC and SRC. This issue has been referred in our revised "Introduction".

3. The marital status is an important demographic factor of patient baseline characteristics. Given many relevant published papers on SEER database have considered this factor, we also included this variable in our study. As confounders, marital status is correlated with age and gender, but our propensity score matching analysis has well balanced these variables between

the 2 comparison groups (all the $p > 0.05$ after PSM). The Cox proportional hazard model has also adjusted these confounding factors.

4. All the Tables and Figures have been moved to the back of the main document.