Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Prognostic significance of lymphovascular invasion in colorectal cancer and its association with genomic alterations" (ID: 46182). These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the revised manuscript. The main corrections in the paper and the responds to the reviewer's comments are as follow:

(1) Responds to the Reviewers' comments:

Reviewer #1:

Comment: 1.- Congratulations for this paper. Very important and showed the relationship of LVI with worse survival. 2.- Very important manuscript for future investigations. 3.- You have to correct page 7 (second Line) Stage III (you put Stage II, twice). It would be very interesting that you wouls determine the 5 yeaar OS not only globally for LVi and non-LVI but in each stage. For example STAGE I CRC with LVI will have which 5 year OS compared with non LVI. This would help the phicisian to be more agressive in treatment for these cases.

Response: Many thanks for your positive comment. We appreciate you for carefully and patiently reviewing our manuscript and feel very sorry for the writing error. We have corrected "Stage II" to "Stage III" in the revised manuscript. We also have revised the whole manuscript carefully and tried to avoid any grammar or writing error. In addition, the manuscript has been revised by someone with expertise in technical English editing.

Reviewer #2:

Comment: Quite interesting study for an issue that is well described before. The study shows all the inherited problems of these retrospective stile. Some questions to answer.

1. Which model of TNM and grading according to the World Health Organization have the tumors been analyzed?
2. The tumor differantiation grading is the old one.

Response: Special thanks to you for your good comment. In our study, a total of 1219 patients with newly diagnosed, histologically confirmed colorectal adenocarcinoma were included in the retrospective analysis. In the course of this study, we reviewed all the medical data. All the tumors were staged according to the American Joint Committee on Cancer (AJCC) TNM classification (version 8.0) and graded according to the 2010 World Health Organization classification, both of which are currently the most widely used in clinical practice.

We have made specific explanations in the revised manuscript：Tumor was staged according to the American Joint Committee on Cancer (AJCC) TNM classification (version 8.0) and graded according to the 2010 World Health Organization classification.

3. Rectal - colon cancers 50-50 prevalence? Bias?

Response: As we showed in the paper, of the 1219 tumors, 650 (53.3%) were rectal cancers and 569 (46.7%) were colon cancers. Various studies have reported that, compared with Western countries, China showed a higher proportion of rectal cancer. In the 20th century, the proportion of rectal to colon cancers in Chinese patient population was about 1.5:1. However, in recent years, the incidence of colon cancer has been increasing rapidly and the proportion of rectal to colon cancers has been close to 1:1. A study reported by You J *et al* enrolled 1314 patients who underwent CRC surgery at the First Affiliated Hospital of Wenzhou Medical University between 2005 and 2011. Among them, 697 (53.0%) were rectal cancers (PMID: 27027440). Another study reported by Peng F *et al* enrolled 1318 patients who underwent CRC surgery at Fujian Provincial Cancer Hospital between 2000 and 2008. Among them, 706 (53.6%) were rectal cancers (PMID: 27560834). As a result, our study data reflect the current incidence and composition of CRCs in our region.

4. Which criteria do they use for selection of 47 surgically removed sporadic colorectal adenocarcinoma specimens ?

Response: Thank you for arranging a timely review for our manuscript. In our study, 47 surgically removed sporadic colorectal adenocarcinoma specimens were used for array-based CGH analysis. Given the presence of LVI, only 21 tumors with LVI were collected between 2017 to 2018 in our hospital. We also collected 26 tumor samples with non-LVI to serve as control group. In order to reduce the impact of other factors on the analysis results, there was no significant difference in gender, age, tumor site, differentiation or stage between the case and control groups.

5. Why so big differences between these 47 and the first 1219 pat in the LMV percentage?

Response: This study consisted of two parts: clinical research and basic research. The clinical research included 1219 CRC patients from 2007 to 2010 and aimed to evaluate the presence of LVI, as well as its relationship with classical clinicopathological parameters and patients' outcome. Among them, 150 tumors were found to present LVI, with a presence of 12.3%. On the other hand, the purpose of the basic research was to identify the genomic alterations associated with LVI. Of the 47 CRC samples, 21 presented with LVI, and 26 with non-LVI served as controls. To reduce the impact of other factors on the analysis results, there was no significant difference in gender, age, tumor site, differentiation or stage between the case and control groups. Hence, these 47 samples cannot be used to reflect the presence rate of LVI in CRCs.

6. What does they mean that LVI was detected in 150 tumors, with a presence of 12.3% (10.5-14.2%). ?? Two different calulations? Does they mean colon vs rectal??

Response: LVI was observed in 150 of 1219 CRCs. 12.3% was the presence rate of LVI, and 10.5-14.2% was the 95% confidence intervals of the presence. This calculation was performed with SPSS software.

(2) Responds to the Editor's comments:

Thanks very much for your time and consideration. We have made the correction in the revised manuscript according to your constructive comments. We also provide the decomposable figure of figures in a PowerPoint, but some figures (such as the figures

of GO terms, KEGG pathway terms and PPI network) cannot be editable because they were software-generated. In addition, the manuscript has also been revised by someone with expertise in technical English editing. We hope that the revised version will meet with approval.

Once again, thank you very much for your comments and suggestions.

We look forward to your reply about our revised manuscript.

Yours sincerely,
Erjiang Tang