Dear Dr Chen and reviewers,

Thanks for your letter and comments concerning our manuscript entitled "Right- and left-sided colorectal cancers respond differently to traditional Chinese medicine" (Manuscript NO.: 35245). These comments were very helpful to improve our paper, as well as providing important guiding significance to our future research. We have studied the comments carefully and have made corrections, which we hope meet with your approval. The revised portions are marked in red in the paper. The main corrections in the paper and the responses to the reviewers' comments are presented below.

Responses to the comments:

 # Reviewers 1

Question 1. The authors can cite some applicable papers.

Thank you very much for providing us with so many suitable papers. We have cited some of these papers in our manuscript and revised the relevant content in the text mainly on lines 241-250.

Thank you very much for your valuable advices.

 # Reviewers 2

Question 1. The TCM that were administered are not described at all in terms of composition, dose, and frequency of administration.

We would like to extend special thanks to you for your excellent comments. We are very sorry that we didn't show these information clear.

Now this part has been revised according to your suggestion on lines 134-137 and lines 251-257.

Composition and dose: the composition and dose of the herbs were determined by attending physicians on the basis of syndrome differentiation (TCM term) which means that the composition and the dose are not fixed, and that they were modified every two weeks according to changes of patients' symptoms to tailor to patients' distinctive symptom complex at most.

Frequency: the herbs were administered as a decoction twice a day (200 ml a time) lasting for at least six months.

Lastly, in order to adapt to patients individually, the composition and the dose were modified frequently, so the herbs (many different kinds or dose) were difficult to be displayed and analyzed by subgroup in this paper. [1] In the future research, we are going to extract some core herbs and fulfill the work.

Question 2. It is not clear if all patients enlisted in this study received the same chemotherapeutic agents (and/or radiotherapy).

Considering this suggestion, we have performed propensity score matching to balance the distribution of chemotherapy and radiotherapy between groups. The baseline characteristics after propensity score matching were presented in supplementary table 1 and 2, in which the covariants were distributed harmoniously between groups, except radiotherapy in left-sided colorectal cancer group (P=0.014). Kaplan-Meier curves and log-rank tests after propensity score matching has been updated, which further verified our findings (Supplementary figures 5,6,7,8).

Question 3. The patient cohort is comprised by dissimilar disease stages.

Thank you very much for your suggestion. Because the patient cohort comprised dissimilar disease stages, except for the analysis of all patients, we made subgroups of different disease stages (Figures 3,4,5). We then tested our results from the whole patient group by including the TNM stages in the propensity score matching, which effectively balanced the distributions of TNM stages between groups (Supplementary tables 1,2).

Question 4. One way to control and correct for all these factors is to perform multivariate analysis. The authors did that, but have included histodifferentiation, lymph node metastasis and TNM stagein the same model. Most likely many of these variables are correlated and multicollinearity is introduced, which affects the prognostic performance of the model.

It is a constructive suggestion for our research. We are very sorry that we have not offered the results of collinearity diagnosis before multivariate analysis which indicated no muticollinearity among dependent and independent variables. The results of collinearity diagnosis were as follows:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	56.549	4.533		12.474	.000		
	Histodifferentiation	.453	.946	.019	.479	.632	.938	1.066
	Lymph	-1.896	3.355	-.040	-.565	.572	.305	3.274
	TNM	-7.617	2.169	-.242	-3.512	.000	.315	3.175

a. Dependent Variable: DFS

Multivariate regression analyses for left-sided colorectal cancer group.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	63.443	10.433		6.081	.000		
	Histodifferentiation	-1.285	1.676	-.053	-.766	.444	.970	1.031
	Lymph	-2.967	6.878	-.060	-.431	.667	.239	4.183
	TNM	-9.390	4.927	-.266	-1.906	.058	.236	4.238

a. Dependent Variable: DFS

Multivariate regression analyses for right-sided colon cancer group.

Because the status of lymph node metastasis was a section of TNM stage, we excluded the part of lymph node metastasis from multivariate analysis. Results of relevant collinearity diagnosis between variables of histodifferentiation and TNM stage were listed as follows:

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	57.793	3.961		14.589	.000		
	Histodifferentiation	.549	.930	.023	.591	.555	.970	1.031
	TNM	-8.624	1.235	-.274	-6.982	.000	.970	1.031

a. Dependent Variable: DFS

Multivariate regression analyses for left-sided colorectal cancer group.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	66.498	7.644		8.699	.000		
	Histodifferentiation	-1.319	1.671	-.054	-.790	.431	.972	1.028
	TNM	-11.240	2.422	-.318	-4.640	.000	.972	1.028

a. Dependent Variable: DFS

Multivariate regression analyses for right-sided colon cancer group.

The collinearity diagnosis indicated no multicollonearity between those variables. Thus, we updated the results of multivariate analysis in table 2 as follows:

	Left-sided colorectal cancer			Right-sided colon cancer		
	Univariate	Multivariate		Univariate	Multivariate	
	P-value	P-value	HR(95%CI)	P-value	P-value	HR(95%CI)
Gender	0.024a	0.079	0.81 (0.63-1.02)	0.339	0.023 a	0.63 (0.42-0.94)
Age	0.955	0.792	1.04 (0.80-1.34)	0.712	0.612	1.12 (0.72-1.76)
Histodifferentiation	0.648	0.016 a	1.16 (1.03-1.31)	0.685	0.407	1.09 (0.89-1.33)
TNM stage	0.000 a	0.000 a	2.39 (1.96-2.90)	0.000 a	0.000 a	2.63 (1.85-3.72)
TCM	0.000 a	0.000 a	0.53 (0.41-0.67)	0.003 a	0.000 a	0.47 (0.31-0.71)
Diabetes	0.948	0.716	0.94 (0.66-1.32)	0.240	0.200	0.67 (0.36-1.24)
Hypertention	0.650	0.120	1.24 (0.94-1.64)	0.019 a	0.005 a	0.51 (0.31-0.81)
Heart disease	0.710	0.988	1.00 (0.66-1. 50)	0.461	0.155	1.57 (0.84-2.93)
Stroke	0.171	0.091	0.60 (0.33-1.09)	0.681	0.449	1.34 (0.63-2.83)

a$P < 0.05$ statistical difference.

Question 5. The introductory section does not provide any useful information for the reader regarding the use of traditional Chinese medicine as an anticancer approach.

We are very sorry for neglecting of this issue. We have made corrections regarding information about traditional Chinese medicine as an anticancer approach on lines 73-74.

We sincerely appreciate your valuable suggestions!

 # Reviewers 3

Question 1. There is no any information of the traditional Chinese medicine. Must the information of the drug product protect confidentially?

We sincerely appreciate your attention to our work. Information on the drug product does not need to be protected confidentially. According to your suggestion, we have revised this part of text on lines 134-137 and lines 251-257. TCM prescriptions were determined by attending physicians on the basis of syndrome differentiation, and their composition and dose were modified

every two weeks to tailor them to the most distinctive symptom complex. Although those highly individualized TCM prescriptions were furthest adapted to the patients' conditions, the composition and the dose were modified frequently, so the herbs (many different kinds or dose) were difficult to be displayed and analyzed by subgroup in this paper. [1] In the future research, we are going to extract some core herbs and fulfill the work.

Question 2. The authors should describe what criteria distinguish left- and right-sided colorectal cancer.

Thank you very much for your comment on our work. we have addressed this issue in the section "Definitions of LSCRC and RSCC" on lines 141-146.

Question 3. The ambiguous sentence should be rewritten.

We apologize for our negligence. We have checked the text and have rewritten the ambiguous sentences, mainly on lines 55, 57-58, 230.

Specially thanks for your good comments!

Other changes:

1. Lines 199-220: "Because of their distinct biological characteristics, LSCRC and RSCC tend to be treated separately." was added.

2. Lines 236-241: the statement "Although the reasons why RSCC responds better to TCM than LSCRC in our study remain unclear, differences between LSCRC and RSCC regarding embryological origin, blood supply, morphology, carbohydrate antigens, etc., should be considered." was corrected as "Whether due to differences in biological characteristics between the two

sides or TCM producing a relatively better effect on RSCC, RSCC exhibited a greater benefit from TCM than LSCRC in our study; this finding is worth further study. Thus, differences between LSCRC and RSCC regarding embryological origin, blood supply, morphology, carbohydrate antigens and other factors should be considered."

3. Lines 241-246: the statement of "RSCC was proven to be more commonly associated with poor prognostic factors such as RAS and BRAF mutations, CpG island methylator phenotype (CIMP)-high, mutagenic metabolites of cytochrome p450, MAPK signaling and mucinous histology. In addition, a high frequency of MSI was observed in RSCC, which has predicted a better outcome for tumors in many but not all studies." was corrected as "In addition, RSCC was more commonly associated with RAS and BRAF mutations, a high CpG island methylator phenotype (CIMP), mutagenic metabolites of cytochrome p450, MAPK signaling and MSI, whereas LSCRC was associated with APC, K-ras, DCC, p53 mutant EGFR signaling, Wnt signaling, and HER1 and HER2 amplification, which played a vital role in cancer generation and progression"

4. Lines 268-269: "Thus, TCM was recommended to postoperative patients with CRC of both sides, especially the right side." was added.

5. Lines 269-270: the statement of "Further studies are necessary to clarify the mechanism of the different responses of primary tumor location to TCM." was corrected as "The mechanism of the different responses of primary tumor location to TCM is worthy of further study."

7. Line 253-255, the sentence of "The interactions between primary tumor location and TCM effectiveness should be evaluated to provide more personalized treatments." was deleted.

8. According to the guidelines of *World J Gastroenterol*, we have added a "comments" section before the references.

9. Since we have cited some papers in our study, the relevant quotation marks have been adjusted.

10. We have modified the language to make it read more like native English.

We tried our best to improve the manuscript and made some changes to the manuscript. These changes do not influence the content or framework of the paper. Changes that we did not list here are marked in red in the revised paper.

We deeply appreciate your helpful input and hope that the corrections will be met with approval.

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

Reference

[1] **Teschke R**, Wolff A, Frenzel C, Eickhoff A, Schulze J. Herbal traditional Chinese medicine and its evidence base in gastrointestinal disorders. *World J Gastroenterol* 2015;**21**(15):4466-90 [PMID: 25914456 DOI: 10.3748/wjg.v21.i15.4466]