To the Editorial

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Based on the comments/suggestions, we have revised our Manuscript. In our response to the Reviewers, We have listed all the responses for the raised questions. All the changes in Manuscript have been highlighted.

To the Reviewer 1 (03018154):

Thank you very much indeed for the very detailed comments, suggestions and criticisms. We have revised our manuscript in details. We hope that our corrections will meet the requests that you have enlisted in your review.

Comments to the author:

1. The prognostic value of PNI in CRC has been elucidated in many studies in recent decades, how this study gives new insights into this issue?

Answer 1: Indeed, there has been a large number of studies investigating influence of PNI on prognosis of CRC patients, however in recent years smaller number of studies have investigated influence of PNI in patients with RC alone. Furthermore our study investigated influence of both PNI and LVI together in early and intermediate RC stages, while previous reports mainly focused on advanced RC stages. Additionally to the best of our knowledge, this is the first study concerning this matter in our country, which is one of the regions with European highest incidence of RC.

2. How did the pathologists detect PNI and LVI in this study? Sometimes, detection of PNI and LVI is quite difficult with H&E stained sections, and mistakes might be made. For this reason, immunohistochemical staining should be employed to detect PNI and LVI precisely.

Answer 2: In our study PNI and LVI were detected using routine H&E staining (Page 6). We thank the reviewer for the comment and suggestion, as he/she is right, sometimes it is difficult to distinguish tumor cells from stroma and normal perineural space, as tumor cell occasionally can show only delicate signs of atypia. According to our pathologist immunohistochemical staining was used in this study only in the ambiguous cases when there was pathological suspicion for PNI since the costs of this method are excessive.

3. This study concluded that adjuvant therapy should be reserved for patients with PNI and LVI in order to improve prognosis. To reach this conclusion, the impacts of adjuvant therapy on survival rates of these patients ought to be investigated, but this study did not provide such data.

Answer 3: We agree with the reviewer, we have changed the conclusion accordingly (Page 10, Paragraph 4). Certainly more randomized prospective studies are necessary to validate our results and to reach conclusion like previous.

To the Referee 2:

We thank the referee for his/her very constructive ideas and suggestions. We have taken into account all of them, and in that way our revised manuscript that it may more suitable for publication.

Comments to the author:

1. I recommend that the authors increase the recurrence-free survival (RFS) rate and the distance failure-free survival (DFFS) rate. And further analyze association between perineural invasion (PNI) and recurrence or metastasis using Chi-square test.

Answer 1: We thank the reviewer and we have made the changes according to his/her's proposition (Results section, Page 8).

To the Referee 3:

We thank the referee for his/her very constructive ideas and suggestions. We have taken into account all of them, and in that way our revised manuscript that it may more suitable for publication.

Comments to the author:

1. Introduction should be slightly modified (too many forms like "Bearing that in mind").

Answer 1: We thank the reviewer and we have made the changes according to his/her's proposition (Page 5).

2. In the Result section information included in Figures and Tables should be excluded.

Answer 2: We thank the reviewer and we have made the changes according to his/her's proposition (Page 7).

3. Please add the limitations of the study.

Answer 3: We have made the changes according to reviewers proposition (Page 10, Paragraph 3).

4. Try to calculate the disease free survival (DFS) rate in addition to overall survival.

Answer 3: We have made the changes according to reviewers proposition (Page 8).