

Dear editor,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “**Is concomitant radiotherapy necessary under gemcitabine-based chemotherapy in pancreatic cancer?**”. (ID: 10312).

We would like to express our great appreciation to you and reviewers for comments on our manuscript. Those comments are all valuable and very helpful for revising and improving our manuscript. We have studied reviewer’s comments carefully and have made direct revision in the original file named “**Revised manuscript**”, and all the revisions were marked in red in the manuscript. We hope these revisions could meet with the approval of the editors and reviewers. Moreover, we also uploaded a clean version of our manuscript named “**Clean manuscript**” for the reviewers to do further revision. We have tried our best to revise our manuscript according to the comments. Attached please find the clean version, which we would like to submit for your kind consideration.

Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

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Responses to the reviewers’ comments:

**Reviewer 02908243**

**Comment 1:** Why was the literature search done since 1979 (statement on page 4), when the introduction describes correctly, that gemcitabine was introduced in the treatment of pancreatic cancer much later in 1997 ? Maybe just a typing error?

**Responses:** The literature search was actually done since the year 1997, when gemcitabine was introduced in the treatment of pancreatic cancer, instead of 1979. We

have corrected it in the manuscript. Sorry for our mistyping error.

**Comment 2:** Why was a p-value  $<0.1$  accepted as statistically significant (statement on page 5)? In general a lower p-value of  $p < 0.05$  is used as discriminator for statistical significance.

**Responses:** Thank you for your interest in this statistical issue. A meta-analysis refers to methods that focus on contrasting and combining results derived from different studies. Test of the heterogeneity across studies is an essential part of meta-analysis. As the test is poor at detecting true heterogeneity when the cut-off value is set as 0.05, it has been widely accepted that  $p < 0.1$ , instead of  $p < 0.05$ , should be considered statistically significant in the test of heterogeneity (Higgins, et al. BMJ, 2003).

**Comment 3:** Obviously in 3 studies patients had not been treated surgically prior to the beginning of gemcitabine based chemotherapy and or radiotherapy, thus these treatments were used as palliative treatments, but in one study (by Van Laethem) curatively resected patients were treated with gemcitabine alone or in combination with radiotherapy in an adjuvant therapy concept. Maybe, the authors could point out more clearly, that their metaanalysis is done independent of surgical considerations of resectability and their conclusions therefore might be further limited, as surgery certainly has a major impact on survival and complications.

**Responses:** Thank you for your suggestions on the discussion of the limitation. We have supplemented these content in the limitation statement of this meta-analysis.

**Reviewer 00074342**

**Comment 1:** I suggest clarification of the study area: is this about adjuvant treatment or about treating locally advanced disease. Corrections throughout the manuscript as well as title needed.

**Responses:** Thank you for your suggestions on this issue. As you may have noticed that patients in 3/4 included studies had not been treated surgically prior to the beginning of GEM-based CT or RT, these treatments were thus used as palliative

treatments. However, patients were treated with GEM alone or in combination with RT following curative resection in one study (by Van Laethem), which should be considered as an adjuvant therapy. In the present meta-analysis, we pooled data of patients from both of the above clinical situations together in order to provide an overall assessment of RT in the treatment of PC, thus we did not clarify “adjuvant” or “palliative” in the title or main manuscript. And this may be one of the major limitations of this meta-analysis, since surgery certainly has an impact on survival and complications of PC patients. So we have supplemented these content in the limitation discussion.

Besides, we performed sensitivity analysis by including only the participants with locally advanced PC in the present meta-analysis. Therefore, data were also available in the setting of palliative treatment. Despite some limitations exist, this meta-analysis may provide a preliminary assessment of RT in the contribution of PC treatment. And this may help to raise interest and future work to further explore this issue. We hope this explanation can meet your approval.