

Point-to-point response to the reviewers:

Reviewer #1: this topic is interesting, but some comments are highlighted below:

- 1- Comment of the reviewer:
some sentences are repeated in the discussion section.

Response to the reviewer:

Thank you for noticing it. We took repetition out. For example at page 12 this sentence “information about the randomization process is completely missing as well a power calculation” regarding the study by Krook was cancelled, as this was already described previously in the common problem of all studies.

The sentence:

“Nevertheless, even when excluded from the meta-analysis, the overall result of the meta-analysis still confirms improved survival by the administration of adjuvant CTx after curative surgery. Furthermore, by excluding all single studies that show a significant benefit of adjuvant CTx and performing a new meta-analysis of the remaining 16 single studies, which by themselves were not statistically significant, the original finding of a benefit of adjuvant CTx after surgery remains statistically significant. We will come back to this point at the end of the discussion”, was cancelled, as it is repeated at a later point in the discussion.

Thank you very much for noticing it, as the repetitions make the discussion boring.

- 2- Comment of the reviewer:
the statistical view of the authors are (prominent) than the clinical aspect.

Response to the reviewer:

Focus of this manuscript is put on the quality of data, evaluating the validity of single studies that are used in the Cochrane review, which is often the basis for guidelines suggestions. Our main purpose was to underline the importance of a critical appraisal of RCTs, as not only results but also the way by which results are achieved is important. We have made this intention clearer in the abstract and throughout the manuscript.

To answer the clinical question about the use of adjuvant CTx after radical resection for rectal cancer a more extensive literature research is mandatory, rather than the solely critical analysis of three studies included in a Cochrane review. In future, we aim to consider a larger amount of literature in order to deal properly with the clinical aspect, which is the most important one. Clinical recommendations rely on results of a large amount of studies and meta-analyses, and if these are not valid, the clinical aspect also lost its importance.

- 3- Comment of the reviewer:
some limitations as regards the bias and a small number of studies interact with conclusions of this review.

Response to the reviewer:

A total of 21 studies were included in the originally meta-analysis by Petersen et al. This is a good number of studies. We analyzed three studies (out of a total of 5 studies which found a statistical significant advantage of adjuvant chemotherapy after curative resection for rectal cancer), because these three had the higher statistical weight and for this reason influenced the result of the meta-analyses conducted by Petersen et al. most. We did not analyze the 16 studies which didn't find any survival advantage of chemotherapy, because our focus was on the statistically significant studies. After exclusion of the 5 statistical significant studies, the result of the meta-analysis still remains significant in favor of chemotherapy. This is an important point to consider, because the quality of a SR and/or MA is highly dependent on the quality of the studies included. [REF: Glaser AN. High-yield biostatistics, epidemiology, and public health. 2014]. In fact, meta-analysis cannot always overcome the limitations of individual trials by pooling treatment effect estimates to generate a single best estimate. The original studies can still be biased, even if meta-analytic methods are perfect. Meta-analysis can usually increase precision (reduce variability), but precision alone does not make up for bias in the component studies [REF: Berlin JA, Golub RM. Meta-analysis as Evidence. Building a Better Pyramid. Jama 2014; 312(6):603-605]. A meta-analysis can often find a statistically significant result just because of the increase of sample size independently from the quality of the included studies [Manzini G, Henne-Bruns D, Kremer M. Validity of studies suggesting post-surgical chemotherapy for resectable gastric cancer: critical appraisal of randomized trials. BMJ Open Gastroenterol 2017. Sep 14, 4(1)].

- 4- Comment of the reviewer:
the 3 line tables are recommended.

Response to the reviewer:

Thank you for remarking this. We changed the three tables accordingly

- 5- Comment of the reviewer:
some grammar and sentence style and structure are highlighted with red color in the uploaded file.

Response to the reviewer:

Thank you very much for the corrections. We corrected sentences and words marked with red color.

The sentence:

“If more than one primary endpoint is present, the power calculation should be adjusted. This study is substantially underpowered limiting its clinical reliability”

Was changed in:

“It is not possible to understand if sample size is high enough, as this should be calculated on the basis of the primary endpoint, which is not clearly defined”

The sentence:

“The indication for CTx was decided by each clinician after consultation with the patient, rather than by any per-protocol definition”.

Was changed in:

“This means that the indication for CTx was decided by each clinician after consultation with the patient”.

“Elegibility” was substituted by “eligibility”; “apparantly” was changed in “apparently”; “mytomycin” was changed in “mitomycin”; “Titel” was substituted by “title” and “Objektives” by “objectives”

- 6- despite the native language of the study is American English, many British English are present in the review.

Thank you for noticing it. The manuscript has been adjusted accordingly.

Reviewer #2: The authors need to address clearly only one issue. The purpose of this study is unclear whether it was used to investigate the benefits of adjuvant chemotherapy in terms of survival or to catch errors for three influential publications. Most of the author's descriptions focus on explaining the benefits of adjuvant therapy in non-metastatic rectal cancer, but it also highlighted the risk of unreliable meta-analysis and the unmet use by errors in previous publications. Therefore, there is considerable ambiguity for the reader to understand the author's intention. This reviewer recommends that the authors revise the related parts throughout the content, including the purpose and conclusion of abstract.

Response to the reviewer:

Thank you for this remark. Reviewer 1 also made a similar comment “the statistical view of the authors are (prominent) than the clinical aspect”. We made our purpose more clear in the abstract (aim) as well as at the end of the introduction and at the beginning of the discussion section. This point was additionally described as limitation of our study. Our paper concentrates on the methodology used to achieve results and analyzes three studies of a Cochrane review, which is not enough to take a position regarding the use or not of adjuvant chemotherapy for rectal cancer operated for cure. For the future, we aim to consider larger amount of data in order to treat exhaustively the clinical aspect. For this manuscript, the purpose was to invite everyone to critically interpret not only the results but also the methodology by which the results were achieved.

Reviewer #3: This is an excellent survey. The content of the article as well as the number and the quality of Tables is adequate. Only a few grammatical errors should be corrected.

Thank you very much for the encouraging comment. The grammatical errors were corrected. We apologized for that.