

Response to Reviewer 1 Comments

1. Summary

Thank you very much for taking the time to review this manuscript. Please find the detailed responses below and the corresponding revisions/corrections highlighted in the re-submitted files.

2. Questions for General Evaluation	Reviewer's Evaluation	Response and Revisions
Does the introduction provide sufficient background and include all relevant references?	Can be improved	The introduction was revised according to the comments.
Is the research design appropriate?	Yes	
Are the methods adequately described?	Can be improved	The statistical methods section was improved according to the comments.
Are the results clearly presented?	Can be improved	The results section was revised according to the comments below.
Are the conclusions supported by the results?	Can be improved	The discussion was revised according to the comments.
Are all figures and tables clear and well presented?	Yes	

3. Point-by-point response to Comments and Suggestions for Authors

Comments 1: Introduction

Line 64 authors wrote: "...that avoid surgery and its substantial morbidity..." This statement is somewhat loaded. Surgery indeed carries an inherent risk of postoperative complications. However, in specialized colorectal surgery centers, the rates of postoperative complications are acceptable, as are the rates of curative oncological resection, maintaining a favorable risk-benefit ratio for rectal cancer patients. It is reasonable to assume that avoiding surgical resection provides the direct benefit of not having to deal with inconveniences, such as time away from work, postoperative recovery, costs, postoperative pain, scars, and long-term issues, such as bowel dysfunction. Nonetheless, this would not amount to substantial morbidity. It would be better if the authors replaced the statement with an objective report on the rates of postoperative complications to be avoided by non-operative management.

Response 1: Thank you for pointing this out. We have now replaced this statement and added an objective reference on the rates of postoperative complications. (<https://doi.org/10.1111/codi.14376>). In this international multicenter study the overall complication rate was 38.8%, and major complications (Clavien grade ≥ 3) rate was 11.8%. This change can be found on page 2, first paragraph, line 64.

Comments 2: Statistical analysis

All statistical methods need to be reported here. The Cox regression needs to be reported as well

Response 2: We appreciate the reviewer's valuable comment. In response, we have revised the Methods section to include a comprehensive description of all statistical analyses performed in the study. Specifically, we added the Cox regression analysis. We hope this addresses the reviewer's concern. See page 4, lines 123-137.

Comment 3: Results

Line 163, the authors wrote: "the pCR group had their stoma reversed later on (79.2% versus 60% among the non-pCR group, $p=0.009$).". This is confusing. You are reporting a rate, not a time frame, so it makes no sense. What do you mean by later? What is the specific time frame?

Response 3: Thank you for pointing this out. We agree that the original phrasing was unclear. Our intention was to report the proportion of patients who eventually underwent stoma reversal, rather than the timing of the reversal. To clarify this, we have rephrased the sentence in line 163 to: "A greater proportion of patients in the pCR group had their stoma reversed compared to the non-pCR group." We have removed the word "later" to avoid any confusion regarding timing, as specific timeframes were not analyzed in this context.

Comment 4: Line 165/166 authors wrote: "but on the other hand, there were 165 less robotic procedures among them (20.8% versus 29.5% respectively, $p=0.2$).". This cannot be asserted, as the p-value of 0.2 is not significant.

Response 4: Thank you for your comment. We agree that the original phrasing may have implied a significant difference. We have revised the sentence to clarify that although the rate of robotic surgery was lower in the pCR group, this difference did not reach statistical significance ($p=0.2$). The revised sentence in line 165 now more accurately reflects the data and avoids any overinterpretation. See page 6, line 166.

Comment 5: 3.5 Long-term oncological outcomes. The authors describe overall survival in the methods section and perform Kaplan-Meier analysis for overall survival. Therefore, they need to maintain consistency and report Cox regression for overall survival as well.

Response 5: We appreciate the reviewer's valuable comment. In response, we have revised the Methods section to include a comprehensive description of all statistical analyses performed in the study. Specifically, we added the Cox regression analysis. (page 11, line 212, and Table 6). We hope this addresses the reviewer's concern.

Comment 6: Lines 213-214. The Authors wrote: "The risk for disease recurrence is increased by 14% for each single lymph metastasis. For every 1 unit rise in CEA levels the risk for disease recurrence is increased by 1.3%. A rise of 10 units in CEA is increasing the recurrence risk by 13%."

You cannot directly assume constancy just because you used the Cox regression. How was the constant hazard increase assessed? Is the proportional hazard assumption met? Alternatively, keep it simple and state that the hazard was 12% (not 14%) higher for an increase in positive

lymph nodes. Same for CEA.

Response 6: Thank you for your insightful comment. We agree that the initial interpretation implied a constant hazard increase, which is not appropriate without formally assessing the proportional hazards assumption and the linearity of continuous predictors. We have revised the paragraph accordingly to directly report the hazard ratios without extrapolating percent increases. The revised text in line 215 now reflects a more accurate and cautious interpretation of the Cox regression findings.

Comment 7: Discussion

Although well-organized and well-written, the discussion of the most interesting aspect of this study was dull and brief. There is evidence that lower rectal cancer has a higher incidence of local recurrence. Therefore, the finding that higher tumors have higher pCR rates, hence long-term outcomes, is appropriate. The discussion could expand this briefly with considerations for anatomy, tumor biology, and microenvironment. This would make for a more contemporary and engaging discussion for the readership.

Examples:

<https://doi.org/10.3390/cancers15245853>

<https://pubmed.ncbi.nlm.nih.gov/29414633/>

Response 7: We appreciate this comment. We have expand our discussion accordingly regarding contemporary predictors for pCR referring to a recent systematic review which you suggested (<https://doi.org/10.3390/cancers15245853>). Key findings of predictors in this review included biochemical predictors such as genetic mutations, clinical predictors including sarcopenia, hypoalbuminemia, and clinical stage at diagnosis, and patient demographics including age, and the order of therapy sequence in TNT. However, the authors concluded that the overall quality of evidence was generally low, and currently there is not enough data to enable accurate prediction of pCR. See page 13, line 290.

4. Response to Comments on the Quality of English Language

Point 1: the English is fine and does not require any improvement

Response: Thank you