Peer Review File

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Reviewer A

This is a retrospective study of patients with locally advanced rectal cancer who receive neoadjuvant treatment. Whilst the paper is well written, and the data that the authors choose to include is comprehensive, I struggled to know what new information the authors have found with this study. The discussion of the various assessments used to try and predict prognosis is very interesting, and well argued, but the data in this paper do not add to the discussion. As the authors admit, it is a very small study in comparison to other, randomized studies. Therefore it is not surprising that there are no new findings.

The parts of the paper that include information about the pattern of tumour response (e.g. fragmentation) - the introduction and the discussion - are interesting, but there are no data that relate to this in the results section. The authors conclude by saying more research is needed in this area. I agree, but we know that without reading this paper. Again, what has the paper added to that topic?

One last, small point. The authors describe the patients as having non-metastatic rectal cancer. Many of their patients had lymph node metastases, so this description is not quite correct. The authors must mean rectal cancer without distant metastases.

In summary, the paper has a good description of the treatment and outcomes of a small group of patients with advanced rectal cancer, with a very good discussion of how response to neoadjuvant treatment can be analysed. However I think it does not bring anything new to the field of study.

We agree with the Reviewer, and further emphasize in the discussion that our results are limited by the retrospective nature of the study. However, we do believe that our data highlights the prognostic heterogeneity that exists within various response categorizations, as well as the relative importance of tumor regression grading irrespective of TN downstaging. To account for discordance of pathologic endpoints (TN downstaging/TRG), the histologic concept of fragmentation and shrinkage are presented as patterns of treatment response in residual tumor that may accounts for the variability in prognosis. We agree this concept requires further study and formalization. We believe these variations in tumor response designated by histologic TNM staging or TRG should not be considered alone since morphologic and biologically relevant information is only partially reflected in these schemas. Our data, albeit limited by patient number and events, indicate that poor tumor response (AJCC TRG3) irrespective of pTN strongly influences oncologic outcome. Similarly, the subset of patients clinical T3 and remaining ypT3 following CRT and total mesorectal excision demonstrated the worse outcome among the AJCC 3 TRG group. These findings highlight the morphologic heterogeneity of these tumors to CRT, and strongly suggest that TN staging should be considered along with TRG for accurate prognosis. In addition, the discrepancy in outcomes among cT=ypT3 with variable TRG's suggests tumor response occurs by different and/or overlapping mechanisms (fragmentation vs shrinkage).

In addition, we have clarified the inclusion criteria for the present study within the abstract and methods sections, stating that patients in the present study had stage II-III rectal cancer without evidence of distant metastasis (lines 120-121, page 4).

Reviewer B

I would like to thank the authors for this well written case series reporting on the association regarding survival and TRG following surgery post nCRT. It is well established that TRG 3 or minimal response correlates with survival and referenced in landmark trials as published by Fokas et. al. which the authors have referenced. I get the sense that the authors want to convey that not just the grade of TRG but the pattern of tumour regression is important.

1) The author should expand more on the inclusion criteria i.e. did all patients have pre-treatment MRI? Did anyone undergo watch and wait initially? If so, did any of them proceeded for salvage surgery in this group? What was the criteria for nCRT?

We agree with the Reviewer. Pre-treatment rectal protocol MRI was incorporated into the institutional protocol in 2014, so patients treated from 2007 to 2014 underwent pre-treatment endorectal ultrasound, and all patients treated from 2015 to 2018 underwent pre-treatment rectal protocol MRI. This has been added to the inclusion criteria discussion within the Methods section in the first paragraph (lines 121-124, page 4).

2) Were there any changes to protocols, treatment regimes, pathological assessments during these period of 2007 - 2018? I suggest some clarity regarding this in the manuscript.

There were no changes to the treatment or pathologic assessment protocols over this duration of time. There were changes to the pre-treatment imaging work up (see response to point 1 above).

3) Further emphasis should be made on the pathology review section to discuss TRG grading and the author's definition of shrinkage versus tumor fragmentation.

The concept of tumor shrinkage versus fragmentation, while discussed in several recent rectal cancer studies, is not well-described or standardized. In our pathologic analysis, we did not differentiate between the shrinkage and fragmentation response pattern. We do discuss these concepts in the discussion (lines 199-214, page 7), and we have added to that discussion.

4) 91% of patients had adjuvant treatment, did this include the 4 patients with TRG 3?

Yes, all 4 patients with TRG 3 received adjuvant chemotherapy, and this has been included in updated manuscript within the Clinical Outcomes section of the results (line 168, page 6).

5) It should also be acknowledged in the discussion, that 21% of resections had no mesorectum evaluation and this could also be a major confounding factor.

We agree with the Reviewer, and we have added this to the limitations within the discussion (page 8, paragraph 7, line 243).

6) On the KM curve, the authors have merged TRG 0 - 2 and is there a specific reason for this given that there are larger number of patients in these individual group?

We have updated Figure 2 to depict the disease-free survival by TRG group on an individual-level (TRG 0 vs TRG 1 vs TRG 2 vs TRG 3).