Peer Review File

Reviewer A
Comment 1:
A very interesting and potentially practical paper for daily clinical practice.
The authors shed light on another prognostic/stratifying factor in RC patients.
Exploring CEA density as a prognostic parameter was very reasonable as the authors stated. Moreover, tumor volume itself, was shown to be a predictive marker for pathological response after neoadjuvant chemoradiotherapy (Lutsyk M, Awawda M, Gourevich K, Ben Yosef R. Tumor Volume as Predictor of Pathologic Complete Response Following Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer. Am J Clin Oncol. 2021 Sep 1;44(9):482-486. doi: 10.1097/COC.0000000000000846. PMID: 34269693.)

Reply 1: Thank you for your valuable comments. Tumor volume is an effective indicator for treatment response evaluation and prognosis prediction. We firmly believe that research on tumor volume will delve deeper.

Comment 2:
The weakness of the study that it did not integrate neoadjuvant (chemo)radiotherapy in the treatment paradigm of the study cohort. As we all know, locally advanced rectal cancer should not undergo upfront surgery unless there are good reasons for peroptreatment omission. Hence, the implications of the findings for stage II-III RC patients are questionable.

Reply 2: Thank you for your valuable comments. As you mentioned, the standard therapy for locally advanced rectal cancer includes concurrent chemoradiotherapy followed by surgery and adjuvant therapy. However, the question of whether all patients could potentially benefit from neoadjuvant therapy remains a significant clinical concern. It has been suggested that some patients at lower risk of local recurrence (eg, proximal rectal cancer staged as T3, N0, M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy. Our subsequent research aims to determine whether CEA/tumor volume can serve as an indicator for exempting low-risk stage II-III RC patients from neoadjuvant therapy.

Comment 3:
I would advise the authors to revise the manuscript in terms of language and grammar.

Reply 3: Thank you for your valuable comments. We thoroughly reviewed and revised the manuscript to improve its language and grammar. We aim to ensure that our work is presented in the most professional and comprehensible manner possible.
Changes in the text: Line 85-87, 91-93, 164, 205, 321

Reviewer B

Comment 1:

excellent work. Enjoyed while reviewing it. few queries for authors

1. what are clinical implications/role of CEA/Vol$_{mri}$ in decision making ? will you offer neoadjuvant chemo/CRT for high CEA/Vol$_{mri}$?

Reply 1: Thank you for your valuable comments. Neoadjuvant strategy is a complex issue that depends on various factors, including the patient's health, the stage of the disease, and the like. In our study, we have observed a certain association between CEA/tumor volume and prognosis. CEA/tumor volume may be valuable for the comprehensive evaluation of rectal cancer.

2. You mentioned that you did not include patients with neoadjuvant chemotherapy and/or radiotherapy. Can you elaborate how results could have been biased if you would include these pts.

Comment 2:

Reply 2: Thank you for your valuable comments. Neoadjuvant therapy for rectal cancer could potentially lead to tumor shrinkage, which means the tumor size measured on pretreatment MRI may not match that measured on postoperative pathology. One important aspect of our research is to compare the pre-CRT tumor size on MRI and pathological tumor size (post-CRT). Therefore, it is necessary to ensure that there is no significant change in tumor size between MRI preconditioning and surgery. The limitation section of the article has been revised.

Changes in the text: Line 314, 315.

Comment 3:

3. Could we use the spherical formula $(4 \times \pi \times \text{radius}^3)/3$ to represent the tumor volume? instead of pixel x slice thickness x voxel size?

Reply 3: Thank you for your valuable comments. The spherical formula $(4 \times \pi \times \text{radius}^3)/3$ can be effectively used to simplify tumor volume estimation for spherical or ellipsoidal lesions. Considering the infiltrative and irregular growth of rectal cancer, as illustrated in supplemental Figure S1, we estimated tumor volume by using pixel * slice thickness * voxel size.