

List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Radiomics for predicting perineural invasion status in rectal cancer" (ID: 68728). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval.

Reviewer #1 (ID 05061662):

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

1. **Response to comment:** Is there a conceivable risk of bias including in the analysis upper and mid-lower rectal cancer together? They differ in imaging evaluation, and outcomes [1] . [1] Clancy C, Flanagan M, Marinello F, O'Neill BD, McNamara D, Burke JP. Comparative Oncologic Outcomes of Upper Third Rectal Cancers: A Meta-analysis. Clin Colorectal Cancer. 2019 Dec;18(4):e361-e367. doi: 10.1016/j.clcc.2019.07.004. Epub 2019 Jul 11.

Response: Thanks for your suggestion. We agree with that upper third rectal cancer has reduced local and distant recurrence rates when compared with mid and lower rectal cancer (RC). Thus, we added a subgroup analysis based on the location of RC in the revised manuscript. The results showed that the performance of the combined model was stable for predicting perineural invasion in upper and mid/lower RC (in upper RC group, AUC = 0.817 [95%CI: 0.730-0.885]; in mid/lower RC group, AUC = 0.824 [95%CI: 0.764-0.875]) . So the model was suitable for both upper and mid/lower RC.

2. **Response to comment:** The authors refer to the evaluation of EMVI and LVI as research perspectives using radiomics or deep learning. However, these parameters are well evaluated with MRI. What about CT-scan?

Response: Several studies have showed that EMVI can be well evaluated with MRI and CT. However, intramural lymphovascular invasion (LVI) cannot be determined by MRI and CT. Thus, we revised "Research perspectives" to the following sentences: Other biological characteristics besides PNI are also related to the prognosis of RC patients; for instance, intramural

lymphovascular invasion (LVI). Intramural LVI cannot be determined by MRI and CT scanning. Thus, using radiomics or deep learning to predict intramural LVI of RC is valuable in the future.

3.Response to comment: A minimal typo pg 5 line 4 (“Figure 2”).

Response: It was modified as required.

Reviewer #2 (ID 02728463):

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

1.Response to comment: First, how was rectal cancer defined at your hospital (for ex.is it 12cm or 15.16 cm from the anal verge)? What is high, or mid/low rectal cancer?

Response: In our hospital, the location of the tumor is categorized as low (0-5 cm from the anal verge), middle (5.1-10 cm from the anal verge), and high (10.1-15 cm from the anal verge). We added this sentence to Table 1 in the revised manuscript. High rectal cancer and mid/low rectal cancer differ in local and distant recurrence rates. We also added a subgroup analysis to evaluate the applicability of the model for high rectal cancer and mid/low rectal cancer.

2.Response to comment: What is the initial work up of your RC patients? Is CT scan a standard initial work up for the RC? and not MRI?

Response: Thanks for your suggestion. In our hospital, the standard imaging modality of patients with clinically suspected rectal cancer is chest-abdomen-pelvis enhanced CT (detecting primary and metastatic lesions) combined with rectal MRI. In this study, preoperative CT and MRI were both performed on about 80% RC patients, and up to 20% RC patients just accepted CT scanning due to: (1) the purpose of saving money and time, and (2) contraindications to MRI examination.

3.Response to comment: What is the standard treatment for patients with RC at your hospital? How would it change the treatment plan if PNI diagnosed preoperatively?

Response: PNI is an established prognostic factor in RC. Not only in RC, but also in many other malignancies like cancer of the oesophagus, bile duct, colon, and prostate cancer, PNI is a prominent finding. In our hospital, RC patients with cT3 and/or cN1-2 are recommended to accept neoadjuvant therapy followed by surgery, while some of them give up neoadjuvant therapy. Preoperative prediction of PNI help clinicians to predict the prognosis of RC patients more accurately, and PNI+ patients should accept more aggressive treatment; for instance, neoadjuvant therapy.

4.Response to comment: What is the sensitivity and specificity for diagnosing PNI using radiomics?

Response: The sensitivities of the radiomics model were 66.09% in the training cohort and 62.07% in the validation cohort. The specificities of our model were 88.19% in the training cohort and 93.75% in the validation cohort, as shown in Table 3, indicating low false positive rate (namely, low misdiagnosis rate) for detecting PNI. We added these sentences to DISCUSSION.