

Response to reviewers

Reviewer #1: Title: A multi-modal radiomics model to predict treatment response to neoadjuvant chemotherapy for locally advanced rectal cancer. The manuscript deals with an interesting and important argument, the evaluation of treatment response to neoadjuvant chemotherapy for locally advanced rectal cancer. The topic has a clinical relevance since several studies have reported that there were still 7%-37% LARC patients who do not respond to neoadjuvant CRT, which may not only increase CRT-related side effects and economic burden, but also delay the surgery time. The manuscript is well written: the title reflects the main subject of the article, abstract and keywords well summarize the arguments. The methodology is described in detail and is well structured. The discussion is well articulated according to results and the authors have clearly underlined the limitations and drawbacks of the manuscript. A point of strength of the article in my opinion is also the multi-modal nomogram, that could be a useful tool for clinicians to predict the treatment outcome, and thus contribute to personalized selection of patients for neoadjuvant chemotherapy in LARC. The tables/figures are representatives and of good quality. The manuscript cites appropriately the latest and authoritative references.

Reading the manuscript some minor concerns have emerged:

1. Please define Locally Advanced Rectal Cancer in materials and methods.

Response: Many thanks for your useful comments. We have added the definition of locally advanced rectal cancer in the **MATERIALS AND METHODS** part by red highlight:

“LARC was defined as the primary tumor invading the muscularized layer of the intestinal wall (T3-4), with or without peripheral lymph node metastasis (N0-2), and without distant metastasis, as detected by imaging or pathological examination. [1]”

Reference 1: Provenzale D, Gupta S, Ahnen DJ, Markowitz AJ, Chung DC, Mayer RJ, Regnbogen SE, Blanco AM, Bray T, Cooper G, Early DS, Ford JM, Giardiello FM, Grady W, Hall MJ, Halverson AL, Hamilton SR, Hampel H, Klapman JB, Larson DW, Lazenby AJ, Llor X, Lynch PM,

Mikkelsen J, Ness RM, Slavin TP, Sugandha S, Weiss JM, Dwyer MA, Ogba N. NCCN Guidelines Insights: Colorectal Cancer Screening, Version 1.2018. *Journal of the National Comprehensive Cancer Network* : JNCCN 2018; 16(8): 939-949 [PMID: 30099370 DOI: 10.6004/jnccn.2018.0067]

2. What is the CRM status of this cohort of patients?

Response: Many thanks for your useful comments. We agree that positive circumferential resection margin (CRM) status on pathology report is considered as a significant factor for worse prognosis (disease-free survival). But for prediction of treatment response to neoadjuvant chemoradiotherapy, TRG grading is often used as the histopathologic reference standard in radiomics model to predict treatment response to neoadjuvant chemoradiotherapy for LARC (References 2, 3, 4). Thus, we prefer TRG grading rather than CRM as the reference standard. But we are also happy to collect and input the CRM data into the paper if indeed necessary.

Reference:

2. Radiomics-Based Pretherapeutic Prediction of Non-response to Neoadjuvant Therapy in Locally Advanced Rectal Cancer *Ann Surg Oncol*, 26 (6), 1676-1684 Jun 2019
3. Pre-treatment ADC image-based random forest classifier for identifying resistant rectal adenocarcinoma to neoadjuvant chemoradiotherapy. *Int J Colorectal Dis*, 35 (1), 101-107 Jan 2020.
4. MR Imaging of Rectal Cancer: Radiomics Analysis to Assess Treatment Response after Neoadjuvant Therapy. *Radiology* 287 (3), 833-843. Jun 2018.

3. According to NCCN guidelines (Benson AB et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*: JNCCN 2018; 16(7): 874-901 [PMID: 30006429 DOI: 10.6004/jnccn.2018.0061]) restaging with MRI should be consider in patients undergone to neoadjuvant chemotherapy. Do any patients perform MRI restaging after neoadjuvant chemotherapy? It could be interesting to find radiomics features for prediction of clinical response also in these patients.

Response: Many thanks for your useful comments. We agreed that the MRI restaging after neoadjuvant chemotherapy is very important to evaluate whether the LARC patients achieve the pathologic complete response (PCR), if yes, which can allow patients to avoid unnecessary surgical intervention. Although MRI/CT after neoadjuvant chemotherapy is performed in all included patients, the main purpose of

our study is to predict the response (yes or no) to neoadjuvant chemotherapy, if yes, the neoadjuvant chemotherapy protocol is worthy to the patients; if not, we should drop the protocol and consider other neoadjuvant treatment protocols (change the drugs or add radiotherapy). Thus, we prefer the MRI/CT before neoadjuvant chemotherapy to construct the radiomics model to predict treatment response for LARC.