**Radiomics analysis of computed tomography for predicting pathological response to neoadjuvant treatment in rectal cancer:** **Post-hoc Analysis of a Randomized Controlled Trial**

Zhuokai Zhuang,1,2,# Zongchao Liu,3,# Xiaolin Wang,2 Peiyi Xie,4 Fei Xiong,4 Juan Li,1,2,5 Jiancong Hu,1,2 Xiaochun Meng,4 Meijin Huang,1,2 Yanhong Deng,2,6 Ping Lan,1,2 Jianping Wang,1,2 Huichuan Yu,2,\*, Yanxin Luo,1,\*

1. Department of Colorectal Surgery, Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, Guangdong, China;

2. Guangdong Institute of Gastroenterology, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Disease, Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, Guangdong, China;

3. Department of Biostatistics, Columbia University, New York, 10032, NY, USA;

4. Department of Radiology, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, 510655, Guangdong, China;

5. Department of Colorectal Surgery, Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, Guangdong, China;

6. Department of Medical Oncology, Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510655, Guangdong, China.

# These authors contribute equally to this work.

\* Corresponding authors

Dr. Huichuan Yu, M.D., Ph.D. Email: [yuhch5@mail.sysu.edu.cn](mailto:yuhch5@mail.sysu.edu.cn)

Address: Guangdong Institute of Gastroenterology, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Disease, Sixth Affiliated Hospital, Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, 510655, Guangdong, China.

Telephone: +86-18302044819

ORCID iD: 0000-0001-8357-1615

Prof. Yanxin Luo, M.D., Ph.D. Email: [luoyx25@mail.sysu.edu.cn](mailto:luoyx25@mail.sysu.edu.cn)

Address: Department of Colorectal Surgery, Sixth Affiliated Hospital, Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, 510655, Guangdong, China.

Telephone: +86-13826190263

ORCID iD: 0000-0002-5200-3997

**Radiomics analysis of computed tomography for predicting pathological response to neoadjuvant treatment in rectal cancer:** **Post-hoc Analysis of a Randomized Controlled Trial**

**Abstract**

**Background:** We aimed to develop a radiomic model based on pre-treatment computed tomography (CT) to predict the pathological complete response (pCR) in patients with rectal cancer after neoadjuvant treatment.**Methods:** This was a secondary analysis of the FOWARC randomized controlled trial. Radiomic features were extracted from pre-treatment portal venous-phase contrast-enhanced CT images of 177 patients with rectal cancer. Patients were randomly allocated to primary and validation cohort. The least absolute shrinkage and selection operator regression was applied to select predictive features to build a radiomic signature for pCR prediction (rad-score model). This CT-based rad-score model was integrated with clinicopathological variables or MRI-based rad-score to construct comprehensive models. The performance of each model was evaluated and compared by receiver operator characteristic (ROC) curve analysis.

**Findings:** We developed a CT-based rad-score model for pCR prediction with areas under curve (AUCs) of 0.925 [95% confidence interval (CI), 0.847-1.000] and 0.950 [95% CI, 0.897-1.000] in the primary and validation cohort respectively. A gradient boosting machine (GBM) model was built after clinicopathological variables were incorporated, with improved AUCs of 0.959 [95% CI, 0.921-0.997] and 0.956 [95% CI, 0.907-1.000] in the primary and validation cohort respectively. Moreover, we constructed a combined model of CT- and MRI-based radiomic signatures that achieved better AUC (0.990 vs. 0.950 vs. 0.949), sensitivity (99.0% vs. 95.0% vs.90.0%) and specificity (99.0% vs. 70.0% vs. 56%) than CT or MRI alone did.

**Interpretation:** The CT-based radiomic models we constructed may provide a useful and reliable tool to predict pCR after neoadjuvant treatment, identify patients that are appropriate for a ‘watch and wait’ approach, and thus avoid overtreatment.

**Key words:** Radiomics, Computed tomography, Neoadjuvant treatment, Rectal cancer

**Research in context**

**Evidence before this study**

Neoadjuvant treatment is considered as the standard treatment for locally advanced rectal cancer (LARC) patients. As the “watch and wait” strategy is recently proposed to be an alternative strategy for patients with clinical complete response, it is urgent to have a reliable method to distinguish pCR before surgery and guide clinical decision making among these patients. There was no research that reported the radiomics analysis of contrast-enhanced CT in pCR prediction for LARC patients with neoadjuvant treatment.

The searching terms on PubMed and Web of Science: “(radiomics OR texture analysis) AND (predict\*) AND (CT OR computed tomography) AND (neoadjuvant) AND (locally advanced rectal cancer)”, not limited to English language publications. The publication dates range from 2015/01/01 to 2020/06/30.

**Added value of this study**

In this post hoc analysis of a randomized controlled trial, we developed multiple radiomic models based on pre-treatment contrast-enhanced CT to predict pCR in LARC patients after neoadjuvant treatment. We also confirmed the predictive value CT-based radiomic signature could add to the MRI-based models that were reported previously and proposed a novel comprehensive model that performed better than CT or MRI alone did.

**Implications of all the available evidence**

Our study suggested radiomics-based models that combined imaging data and clinicopathological variables could well predict response to neoadjuvant treatment in LARC patients. This may guide clinical decision making for ‘watch and wait’ strategy and thus achieve personalized treatment for LARC patients.

**Introduction**

Colorectal cancer is known as the third common cancer in the world, of which 70% are locally advanced rectal cancer (LARC).[1] The current treatment for LARC(T3-4 and/or N+) is neoadjuvant treatment followed by total mesorectal excision (TME) surgery.[2] Among the patients receiving neoadjuvant treatment, roughly 15-27% of patients can achieve pathological complete response (pCR) with no visible tumor cells in the resected tumor specimen.[3] A “watch and wait” strategy could be applied in these patients to achieve comparable survival outcomes with radical resection while avoiding surgical complications, including anastomotic leak, sexual and urinary dysfunction, and severe alteration of bowel function.[3-6]

However, pCR can only be confirmed by evaluating resected specimens after surgery. Therefore, it is essential to identify patients that could achieve pCR with an reliable and non-invasive method before surgery and even before neoadjuvant therapy.[7] Numerous studies have tried to develop optimal predictive panels using clinicopathological characteristics or molecular biomarkers, but they failed to achieve a good sensitivity and specificity to determine treatment response.[8-11] In addition, imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography is non-invasive methods have been exploited to evaluate the therapeutic responses to neoadjuvant.[12, 13] Although they have shown promising value in response prediction, they are limited by their subjective nature and inconsistent evaluation from different radiologist.[14] Therefore, it is urgent to develop methods to better use imaging data in batch mode to stratify patients by their response to neoadjuvant treatment.

Radiomics, a fast-emerging field of image analysis, could extract high-dimension feature information from routinely acquired medical images in a high-throughput way, followed by subsequent data analysis for decision support.[15, 16] These features have been revealed to be closely associated with pathological heterogeneity,[17] prognosis,[18, 19] treatment response,[20] and molecular phenotypes[21, 22] in tumors.

Multiple studies have recently applied radiomics to predict pCR after neoadjuvant treatment in LARC patients.[23-26] However, previous CT-based models for predicting pCR after neoadjuvant treatment turn out to be controversial, which can be attributed to their retrospective design, small size of cohort, and non-contrast CT images that they used.[27, 28] In addition, to our best knowledge, none of previous studies has evaluated the feasibility of combing CT-based and MRI-based radiomic signature to predict pCR.

We therefore aimed to develop and validate a CT-based radiomic model to predict pCR by using prospectively collected imaging data in LARC patients from a randomized controlled trial (FOWARC, NCT01211210) that compared different neoadjuvant regimens[29, 30]. Moreover, we assessed the performance of an integrated model that combines CT-based and T2-weighted (T2W) MRI-based radiomic signature in pCR prediction to better guide the decision making of a “watch and wait” strategy.

**Materials and methods**

**Patients**

The patients enrolled in the FOWARC (NCT01211210) clinical trial[29, 30] were identified and included in this study. Briefly, all the patients were locally advanced rectal cancer (cT3-4 and/or cN1-2, c-Stage II-III), and they were randomly assigned to three neoadjuvant treatment groups as we previously described[29, 30]. Patients in each group underwent curative surgery 6-8 weeks after neoadjuvant treatment. Among these patients, 177 patients with available portal venous-phase contrast-enhanced CT images data using the same CT scanner were included in current study. They were randomly allocated to primary and validation cohort at a ratio of 2:1. The workflow of patient cohort disposition is shown in **Fig.1**. This study was approved by the Institutional Review Board of the Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) with informed consent from subjects.

**Data collection and pathological response evaluation**

Demographic characteristics and baseline characteristics of patients were prospectively collected or obtained from institutional cancer database and inpatient medical records. Pathological response after neoadjuvant therapy was evaluated using the tumor response grading (TRG) system[31] by two pathologists in consensus. Patients were divided into two different response groups: pCR group (TRG 0, no viable residual tumor cells) and non-pCR group (TRG 1–4, varying from rare residual cancer cells to extensive residual cancer cells).

**Image data acquisition and tumor segmentation**

All patients underwent CT scans within one week before neoadjuvant treatment. The imaging data were retrieved from the picture archiving and communication system (PACS, Carestream, Canada). As shown in **Fig.2**, the region of interest (ROI) covering the whole tumor was manually outlined along the margin of tumors by two experienced radiologists using the itk-SNAP software(version 3.8.0, [www.itksnap.org](http://www.itksnap.org)). The robustness of each ROI outlining and inter-/intra-observer reproducibility were evaluated by calculating the intra- and inter-class correlation coefficients (ICCs). Both of the radiologists were blinded to the clinicopathological information of each case.

**Radiomic features extraction**

The radiomic features were preprocessed and extracted by Pyradiomics (Version 2.1.2) as previously described.[32] Two methods of filter were applied to preprocess CT images: Laplacian of Gaussian (an edge enhancement filter that emphasizes areas of gray level change)[33] and Wavelet filtering (a filter yielding eight decompositions per level in each of the three dimensions). Each original image was normalized with z-score before being processed by filters. A total of 1,218 radiomic features were then acquired from CT images in each patient, including the first-order statistics and other statistics derived from the Gray-Level Co-occurrence Matrix (GLCM), Gray Level Run Length Matrix (GLRLM), Gray Level Size Zone Matrix (GLSZM), and Gray Level Dependence Matrix (GLDM).[34] The detailed feature extraction procedure and parameter settings could be found in the supplementary materials.

**Feature selection and radiomic signature construction**

We took multiple steps to identify the pCR-associated radiomic features. First, we evaluated the overall pair-wise correlation and excluded highly correlated features based on the cut-off value (*ρ* = 0.85) to select candidate features for further analysis. Second, a logistic regression model optimized by the least absolute shrinkage and selection operator (LASSO) method was applied to further select representative features that were associated with achieving pCR. Finally, the radiomic signature, termed as rad-score, of each patient was calculated through a linear combination of estimated coefficients and radiomic values of each selected feature.

**Development and validation of the individualized predicting model**

We applied three different methods to integrate rad-score with clinicopathological predictors. The three methods, including logistic regression, random forests (RF), and gradient boosting machine (GBM), were developed and validated as previously described. For the logistic regression model, clinicopathological characteristics with p value less than 0.1 in univariate analysis for the association with pCR were enrolled into the multivariate logistic regression. Backwards stepwise selection was applied with Akaike’s information criterion as the stopping rule. The RF and GBM model included all candidate variables following the Gini split-rule. More information about the models was provided in supplementary materials.

**Development of a model integrating CT- and MRI-based radiomic features**

The pre-treatment T2W MRI images of 99 patients were retrieved from PACS. The tumor segmentation and radiomic signature construction were conducted as they were done in CT image analyses. The integrated radiomic signature (CT-MRI rad-score) was defined as the mean value of the CT-based and MRI-based rad-score for each patient. Performance comparison between the primary model and integrated model were conducted through a resampling method.

**Statistical analysis**

Demographic and clinicopathological characteristics were compared between the pCR and non-pCR groups using *two-sample* *t*-test (for continuous numerical variable) or chi-squared tests (categorical variable) in the primary cohort and validation cohort, respectively. All the statistical analyses were conducted with R software version 3.6.2 (http://www.R-project.org). The model construction, parameter tuning, comparison and assessment were performed by using the “caret” package. The Receiver operating characteristic (ROC) analyses were conducted by using the “pROC” package. Model performance was assessed based on the average area-under-receiver-operator-curve (AUC), accuracy, positive predictive value (PPV), negative predictive value (NPV), specificity, and sensitivity. A decision curve analysis (DCA) of the logistic regression model was conducted to evaluate the clinical practicability by calculating the net benefits at different threshold probabilities. The statistical significance levels were all set to be 0.05 with two sides.

**Role of the funding source**

None declared

**Results**

**Demographic and Clinicopathological characteristics**

The baseline characteristics of patients in the primary cohort and validation cohort were shown in **Table.1**. There were 119 and 58 patients in the primary and validation cohort respectively. Among them, 21 patients (17.60%) achieved pCR in the primary cohort (15 males, 6 females) and 10 patients (17.20%) did that in the validation cohort (6 males, 4 females). There were no significant differences in clinicopathological characteristics between pCR and non-pCR patients in both cohorts.

**Feature selection and radiomic signature construction for predicting pCR**

According to the criterion that features with pair-wise Pearson correlation, the selected features were included into the LASSO regression model and 54 features were finally selected to build the rad-score. The selected features contained 13 first-order features, 7 GLCM features, 4 GLDM features, 5 GLRLM features, 23 GLSZM features, and 2 shape features from 13 different filtrations. Detailed information of the selected features was provided in the supplementary materials. The rad-scores of the pCR group were significantly higher than those in the non-pCR group in both the primary (*P* < 0.001) and validation (*P* < 0.001) cohort. Of note, the distributions of rad-scores in both cohorts were shown in **Fig.3**,in which the majority of patients achieving pCR had a high rad-score in both cohorts. Moreover, rad-score had an AUC of 0.925[95% confidence interval (CI), 0.847–1.000] and 0.950[95% CI, 0.897–1.000] in predicting pCR in the primary and validation cohort, respectively (**Fig.5**).

**Developing and validation of integrated models for predicting pCR**

We further constructed models that integrated rad-score with clinicopathological predictors to better predict pCR. The multivariate logistic regression, RF and GBM models were constructed as shown in **Table.2** and **Fig.4**. In the logistic model, the therapeutic regimens (*p*=0.024) and rad-score (*p*<0.001) were independent predictive variables. The decision curve analysis (DCA) for the logistic regression model confirmed the application of the radiomics predicting model for clinical decision making (**Fig.5**). The top four ranked predictive variables were rad-score, tumor thickness, therapeutic regimens, and CEA in the RF model, while those in the GBM model were rad-score, tumor thickness, therapeutic regimens, and age. Detailed information of these models was given in the supplementary materials.

Next, we compared the three integrated models with rad-score alone in predicting pCR. The RF model and GBM model had better predictive performance than Logistic model or rad-score alone did (**Fig.5**). The RF model had an AUC of 0.992[95% CI, 0.982–1.000] and 0.950[95% CI, 0.897–1.000] in the primary and validation cohort, respectively, while the GBM model yielded an AUC of 0.959[95% CI, 0.921–0.997] in the primary cohort and the highest AUC of 0.956[95% CI, 0.907–1.000] in the validation cohort (**Fig.5**). Moreover, the GBM model had best sensitivities and specificities in both cohorts (**Table.2**). Taken together, we considered the GBM model as the best-performing model.

**CT-based radiomic signature contributes to MRI-based radiomic model**

To explore the values that CT-based radiomic signature could add to previously reported MRI-based radiomic model, we retrieved the pre-treatment T2W MRI images of 99 patients from PACS system and performed radiomic analyses. A total of 34 MRI features were selected, and CT-MRI rad-scores were calculated for each patient in this subset. As shown in **Fig.6B**, the CT-MRI score model yielded higher AUCs than CT-based alone or MRI-based alone model. Moreover, the CT-MRI score could better predict pCR with higher sensitivity and specificity.

**Discussion**

In this post-hoc analysis derived from a prospectively randomized controlled trial, we initially used machine learning methods to construct a pCR-associated rad-score model based on radiomic features extracted from pre-treatment portal venous-phase contrast-enhanced CT images. This CT-based rad-score model had AUCs of 0.925 and 0.950 when it was applied to predict pCR in the primary and validation cohort respectively. We next integrated the rad-score with clinicopathological variables to develop multiple predictive models for pCR. Among the models, we yielded a GBM model with best performance that had AUCs of 0.959 and 0.956 in the primary and validation cohort. Moreover, we integrated the CT-based and MRI-based radiomic signatures to construct an improved model that achieved better AUC, sensitivity and specificity than CT or MRI alone did. The models we constructed may provide a useful and reliable tool to identify pCR patients that are appropriate for a ‘watch and wait’ approach, and thus avoid unnecessary overtreatment.

A total of 1,218 candidate radiomic features were extracted from the primary tumor region and then reduced to a set of 54 representative features that were associated with pCR through the LASSO regression method, a high-throughput machine learning algorithm for analyzing large sets of high-dimensional data to discriminate variables correlating to the target events.[35] The Gray Level Size Zone Matrix (GLSZM) features, which quantify gray level zones (defined as the number of connected voxels that share the same gray level intensity) in an image, accounted for the largest proportion (23/54, supplementary table). These features quantitively reveal the voxel heterogeneity of the segmented images by grey level dispersion and texture alterations. It has been shown that tumors with higher heterogeneity tend to get aberrant values in these radiomic features, which is consistent with the hypothesis that tumor heterogeneity with underlying molecular phenotypes may be associated with treatment responses and prognostic outcomes.[36, 37] The First Order features, including a basic evaluation of voxel intensities, contributed to our radiomic signature as well (13/54, supplementary table). Voxel intensities reflect the shape and volume irregularity of tumors, which are difficult to be identified with naked eyes. Comparing with other studies that applied the features merely from the primary images,[27, 38] we used Laplacian of Gaussian (LoG) and Wavelet filters to preprocess the images into multiple filtered images through different scale of smoothing.[39] Previous studies showed that preprocessing with filters can reduce the hybrid texture of paracancerous tissue and enhance the high-dimensional features of tumors that are difficult to be recognized in directly visual assessment.[40] The high proportion of features from the processed images in the radiomic signature (49/54, supplementary table) confirmed the importance of image filtering before feature extraction.

Considering the values of clinicopathological characteristics in predicting outcomes,[8-11] we combined them with rad-scores to construct comprehensive models. Compared with the logistic model, the tree-based models (RF and GBM model) showed better performance. The tree-based models have been effective and popular due to their interpretability and high accuracy, which can be readily displayed graphically and substantially improved by aggregating single trees (using methods like RF, boosting, or bagging). The RF model decorrelates the trees by forcing each split to consider only a subset of the predictors. The gradient boosted tree-based model is an alternative approach that is recently applied to statistical learning methods for classification problems, which can grow the trees based on previously grown ones. Our results proved that clinical variables have the potential to improve the stratification of pCR possibility in patients with neoadjuvant treatment. It could be anticipated that incorporating variables with more dimensions such as molecular biomarkers may further improve current models.

As the “watch and wait” strategy is recently proposed to be an alternative strategy for patients with clinical complete response (cCR), it is urgent to have a reliable and accurate method to distinguish pCR before surgery and guide clinical decision making among these patients. Considering the predictive value of our radiomic models constructed before treatment for pCR, they could at least assist clinicians to distinguish cCR patients achieving pCR from those not achieving pCR after neoadjuvant treatment. The decision curve analysis (DCA) of the logistic regression model demonstrated that this model might added more net benefit in the clinical practice than the ‘treat all’ or ‘treat none’ strategies as the threshold probability shifting from 0% to 100%. This model could be a quantitative and reliable tool in deciding which patients need radical surgery and which patients are suitable for “watch and wait” strategy.

There have been some recent studies that constructed radiomic models to identify patients that may achieve pCR after neoadjuvant treatment. Among them, most investigated the predictive value of radiomic features for pCR based on multiparametric MRI and the AUCs of these models were reported to be 0.80-0.90.[25, 41, 42] Few of them focused on CT-based radiomics analysis, although it has been demonstrated to facilitate the prediction of lymph node metastasis[43-45] and prognostic outcomes[27] in multiple studies. Previous studies focusing on CT images radiomics analysis for pCR prediction were limited by their retrospective design and imaging heterogeneity.[28, 46] Comparing to these studies, our study enrolled patients from a randomized controlled trial that can better control imbalanced distribution of confounding factors and used the portal venous-phase contrast-enhanced CT images that are commonly approved to be more informative in interpreting tumor tissues. With this predominance, our results add reliable evidence for pretreatment CT-based radiomics analysis in predicting pCR after neoadjuvant treatment. Of note, our CT-based rad-score model had an AUC as high as 0.950, which seemed to be superior to MRI-based models in previous studies.[25, 41, 42] Based on this result, we innovatively explored the additional benefits of CT-based radiomic signatures for previously reported MRI-based models and constructed a novel integrated model. Expectedly, a dramatic improvement was determined in the integrated model with better AUC, sensitivity, and specificity compared to either of them alone. This results also showed that combining CT and MRI images may interpret rectal tumors in a more comprehensive way. This novel modality of predicting model deserves to be further investigated and validated in a large cohort.

The robustness of this study mainly came from the prospective patient cohort and homogeneity of imaging data that were applied in radiomics analysis, though there are some limitations in our study. First, the sample size of patients with pCR was small in our cohorts, which may introduce bias and bring the inaccuracy and instability to the predictive models. Second, this was a secondary study of a clinical trial. A validation of the proposed models in an independent cohort is warranted in further study before clinical application. Third, the integrated model that enrolled CT-based and MRI-based radiomic signatures is and exploratory and preliminary test with limited sample size. The additional studies for model optimization and validation in patient cohorts would be necessary.

**Conclusion**

This post-hoc study of a randomized controlled trial developed and validated a pre-treatment enhanced CT-based rad-score model to accurately predict pCR after neoadjuvant treatment in LARC patients. We further integrated the rad-score with clinicopathological variables to develop a GBM model for pCR prediction with improved performance. Moreover, we explored the predictive value CT-based radiomic signature could add to the MRI-based models that were reported previously and proposed a novel comprehensive model that performed better than CT or MRI alone did. These models could be useful tools to help clinical decision making in rectal cancer patients receiving neoadjuvant treatment.

**Funding sources**This work was supported by the National Basic Research Program of China (973 Program) (No. 2015CB554001, JW), the Project 5010 of Clinical Medical Research of Sun Yat-sen University-5010 Cultivation Foundation (No. 2018026, YL), the National Natural Science Foundation of China (No. 81972245, YL; No. 81902877, HY), the Natural Science Fund for Distinguished Young Scholars of Guangdong Province (No. 2016A030306002, YL), the Tip-top Scientific and Technical Innovative Youth Talents of Guangdong special support program (No. 2015TQ01R454, YL), the Natural Science Foundation of Guangdong Province (No. 2018A0303130303, HY), the Talent Project of the Sixth Affiliated Hospital of Sun Yat-sen University (No. P20150227202010251, YL; No. P20150227202010244, JW), the Program of Introducing Talents of Discipline to Universities, and National Key Clinical Discipline (2012).

**Declaration of Competing Interests**

The authors declare no potential conflicts of interest.

**Author contributions**

Conception and design: ZZ, ZL, HY, YL; Collection and assembly of data: ZZ, ZL, XW, PX, FX, JL, JH, XM, MH, YD, PL, JW, HY, YL; Development of methodology: ZZ, ZL, HY, YL; Data analysis and interpretation: ZZ, ZL, HY; Manuscript drafting: ZZ, ZL; Manuscript revision: HY, YL; Final approval of manuscript: All authors.

**References**

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018. 68(6): 394-424.

[2] Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol. 2018. 23(1): 1-34.

[3] Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017. 2(7): 501-513.

[4] Silva-Velazco J, Dietz DW, Stocchi L, Costedio M, Gorgun E, Kalady MF, Kessler H, Lavery IC, Remzi FH. Considering Value in Rectal Cancer Surgery: An Analysis of Costs and Outcomes Based on the Open, Laparoscopic, and Robotic Approach for Proctectomy. Ann Surg. 2017. 265(5): 960-968.

[5] Hawkins AT, Hunt SR. Watch and Wait: Is Surgery Always Necessary for Rectal Cancer. Curr Treat Options Oncol. 2016. 17(5): 22.

[6] Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, Rooney PS, Susnerwala S, Blower A, Saunders MP, Wilson MS, Scott N, O'Dwyer ST. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2016. 17(2): 174-183.

[7] Smith JJ, Paty PB, Garcia-Aguilar J. Watch and Wait in Rectal Cancer or More Wait and See. JAMA Surg. 2020 .

[8] Tan Y, Fu D, Li D, Kong X, Jiang K, Chen L, Yuan Y, Ding K. Predictors and Risk Factors of Pathologic Complete Response Following Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Population-Based Analysis. Front Oncol. 2019. 9: 497.

[9] Al-Sukhni E, Attwood K, Mattson DM, Gabriel E, Nurkin SJ. Predictors of Pathologic Complete Response Following Neoadjuvant Chemoradiotherapy for Rectal Cancer. Ann Surg Oncol. 2016. 23(4): 1177-86.

[10] Lorimer PD, Motz BM, Kirks RC, Boselli DM, Walsh KK, Prabhu RS, Hill JS, Salo JC. Pathologic Complete Response Rates After Neoadjuvant Treatment in Rectal Cancer: An Analysis of the National Cancer Database. Ann Surg Oncol. 2017. 24(8): 2095-2103.

[11] Ren DL, Li J, Yu HC, Peng SY, Lin WD, Wang XL, Ghoorun RA, Luo YX. Nomograms for predicting pathological response to neoadjuvant treatments in patients with rectal cancer. World J Gastroenterol. 2019. 25(1): 118-137.

[12] Nougaret S, Vargas HA, Lakhman Y, Sudre R, Do RK, Bibeau F, Azria D, Assenat E, Molinari N, Pierredon MA, Rouanet P, Guiu B. Intravoxel Incoherent Motion-derived Histogram Metrics for Assessment of Response after Combined Chemotherapy and Radiation Therapy in Rectal Cancer: Initial Experience and Comparison between Single-Section and Volumetric Analyses. Radiology. 2016. 280(2): 446-54.

[13] Yu J, Xu Q, Song JC, Li Y, Dai X, Huang DY, Zhang L, Li Y, Shi HB. The value of diffusion kurtosis magnetic resonance imaging for assessing treatment response of neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Eur Radiol. 2017. 27(5): 1848-1857.

[14] Gollub MJ, Tong T, Weiser M, Zheng J, Gonen M, Zakian KL. Limited accuracy of DCE-MRI in identification of pathological complete responders after chemoradiotherapy treatment for rectal cancer. Eur Radiol. 2017. 27(4): 1605-1612.

[15] Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology. 2016. 278(2): 563-77.

[16] Kiessling F. The changing face of cancer diagnosis: From computational image analysis to systems biology. Eur Radiol. 2018. 28(8): 3160-3164.

[17] Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Carvalho S, Cavalho S, Bussink J, Monshouwer R, Haibe-Kains B, Rietveld D, Hoebers F, Rietbergen MM, Leemans CR, Dekker A, Quackenbush J, Gillies RJ, Lambin P. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun. 2014. 5: 4006.

[18] Huang Y, Liu Z, He L, Chen X, Pan D, Ma Z, Liang C, Tian J, Liang C. Radiomics Signature: A Potential Biomarker for the Prediction of Disease-Free Survival in Early-Stage (I or II) Non-Small Cell Lung Cancer. Radiology. 2016. 281(3): 947-957.

[19] Kickingereder P, Götz M, Muschelli J, Wick A, Neuberger U, Shinohara RT, Sill M, Nowosielski M, Schlemmer HP, Radbruch A, Wick W, Bendszus M, Maier-Hein KH, Bonekamp D. Large-scale Radiomic Profiling of Recurrent Glioblastoma Identifies an Imaging Predictor for Stratifying Anti-Angiogenic Treatment Response. Clin Cancer Res. 2016. 22(23): 5765-5771.

[20] Liu Z, Zhang XY, Shi YJ, Wang L, Zhu HT, Tang Z, Wang S, Li XT, Tian J, Sun YS. Radiomics Analysis for Evaluation of Pathological Complete Response to Neoadjuvant Chemoradiotherapy in Locally Advanced Rectal Cancer. Clin Cancer Res. 2017. 23(23): 7253-7262.

[21] Xi YB, Guo F, Xu ZL, Li C, Wei W, Tian P, Liu TT, Liu L, Chen G, Ye J, Cheng G, Cui LB, Zhang HJ, Qin W, Yin H. Radiomics signature: A potential biomarker for the prediction of MGMT promoter methylation in glioblastoma. J Magn Reson Imaging. 2018. 47(5): 1380-1387.

[22] Huang C, Cintra M, Brennan K, Zhou M, Colevas AD, Fischbein N, Zhu S, Gevaert O. Development and validation of radiomic signatures of head and neck squamous cell carcinoma molecular features and subtypes. EBioMedicine. 2019. 45: 70-80.

[23] Giannini V, Mazzetti S, Bertotto I, Chiarenza C, Cauda S, Delmastro E, Bracco C, Di DA, Leone F, Medico E, Pisacane A, Ribero D, Stasi M, Regge D. Predicting locally advanced rectal cancer response to neoadjuvant therapy with 18F-FDG PET and MRI radiomics features. Eur J Nucl Med Mol Imaging. 2019. 46(4): 878-888.

[24] Bulens P, Couwenberg A, Intven M, Debucquoy A, Vandecaveye V, Van Cutsem E, D'Hoore A, Wolthuis A, Mukherjee P, Gevaert O, Haustermans K. Predicting the tumor response to chemoradiotherapy for rectal cancer: Model development and external validation using MRI radiomics. Radiother Oncol. 2020. 142: 246-252.

[25] Antunes JT, Ofshteyn A, Bera K, Wang EY, Brady JT, Willis JE, Friedman KA, Marderstein EL, Kalady MF, Stein SL, Purysko AS, Paspulati R, Gollamudi J, Madabhushi A, Viswanath SE. Radiomic Features of Primary Rectal Cancers on Baseline T2 -Weighted MRI Are Associated With Pathologic Complete Response to Neoadjuvant Chemoradiation: A Multisite Study. J Magn Reson Imaging. 2020 .

[26] Zhou X, Yi Y, Liu Z, Cao W, Lai B, Sun K, Li L, Zhou Z, Feng Y, Tian J. Radiomics-Based Pretherapeutic Prediction of Non-response to Neoadjuvant Therapy in Locally Advanced Rectal Cancer. Ann Surg Oncol. 2019. 26(6): 1676-1684.

[27] Wang J, Shen L, Zhong H, Zhou Z, Hu P, Gan J, Luo R, Hu W, Zhang Z. Radiomics features on radiotherapy treatment planning CT can predict patient survival in locally advanced rectal cancer patients. Sci Rep. 2019. 9(1): 15346.

[28] Hamerla G, Meyer HJ, Hambsch P, Wolf U, Kuhnt T, Hoffmann KT, Surov A. Radiomics Model Based on Non-Contrast CT Shows No Predictive Power for Complete Pathological Response in Locally Advanced Rectal Cancer. Cancers (Basel). 2019. 11(11).

[29] Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, Chen D, Cao J, Wei H, Peng X, Huang Z, Cai G, Zhao R, Huang Z, Xu L, Zhou H, Wei Y, Zhang H, Zheng J, Huang Y, Zhou Z, Cai Y, Kang L, Huang M, Peng J, Ren D, Wang J. Modified FOLFOX6 With or Without Radiation Versus Fluorouracil and Leucovorin With Radiation in Neoadjuvant Treatment of Locally Advanced Rectal Cancer: Initial Results of the Chinese FOWARC Multicenter, Open-Label, Randomized Three-Arm Phase III Trial. J Clin Oncol. 2016. 34(27): 3300-7.

[30] Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, Chen D, Cao J, Wei H, Peng X, Huang Z, Cai G, Zhao R, Huang Z, Xu L, Zhou H, Wei Y, Zhang H, Zheng J, Huang Y, Zhou Z, Cai Y, Kang L, Huang M, Wu X, Peng J, Ren D, Wang J. Neoadjuvant Modified FOLFOX6 With or Without Radiation Versus Fluorouracil Plus Radiation for Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Trial. J Clin Oncol. 2019. 37(34): 3223-3233.

[31] Trakarnsanga A, Gönen M, Shia J, Nash GM, Temple LK, Guillem JG, Paty PB, Goodman KA, Wu A, Gollub M, Segal N, Saltz L, Garcia-Aguilar J, Weiser MR. Comparison of tumor regression grade systems for locally advanced rectal cancer after multimodality treatment. J Natl Cancer Inst. 2014. 106(10).

[32] van Griethuysen JJM, Fedorov A, Parmar C, Hosny A, Aucoin N, Narayan V, RGH B, Fillion-Robin JC, Pieper S, HJWL A. Computational Radiomics System to Decode the Radiographic Phenotype. Cancer Res. 2017. 77(21): e104-e107.

[33] Kong H, Akakin HC, Sarma SE. A generalized Laplacian of Gaussian filter for blob detection and its applications. IEEE Trans Cybern. 2013. 43(6): 1719-33.

[34] Zwanenburg A, Vallières M, Abdalah MA, HJWL A, Andrearczyk V, Apte A, Ashrafinia S, Bakas S, Beukinga RJ, Boellaard R, Bogowicz M, Boldrini L, Buvat I, GJR C, Davatzikos C, Depeursinge A, Desseroit MC, Dinapoli N, Dinh CV, Echegaray S, El NI, Fedorov AY, Gatta R, Gillies RJ, Goh V, Götz M, Guckenberger M, Ha SM, Hatt M, Isensee F, Lambin P, Leger S, RTH L, Lenkowicz J, Lippert F, Losnegård A, Maier-Hein KH, Morin O, Müller H, Napel S, Nioche C, Orlhac F, Pati S, EAG P, Rahmim A, AUK R, Scherer J, Siddique MM, Sijtsema NM, Socarras FJ, Spezi E, RJHM S, Tanadini-Lang S, Thorwarth D, EGC T, Upadhaya T, Valentini V, van Dijk LV, van Griethuysen J, van Velden FHP, Whybra P, Richter C, Löck S. The Image Biomarker Standardization Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping. Radiology. 2020. 295(2): 328-338.

[35] Lee S, Seo MH, Shin Y. The lasso for high dimensional regression with a possible change point. J R Stat Soc Series B Stat Methodol. 2016. 78(1): 193-210.

[36] Bettoni F, Masotti C, Habr-Gama A, Correa BR, Gama-Rodrigues J, Vianna MR, Vailati BB, São JGP, Fernandez LM, Galante PA, Camargo AA, Perez RO. Intratumoral Genetic Heterogeneity in Rectal Cancer: Are Single Biopsies representative of the entirety of the tumor. Ann Surg. 2017. 265(1): e4-e6.

[37] Imperial R, Ahmed Z, Toor OM, Erdoğan C, Khaliq A, Case P, Case J, Kennedy K, Cummings LS, Melton N, Raza S, Diri B, Mohammad R, El-Rayes B, Pluard T, Hussain A, Subramanian J, Masood A. Comparative proteogenomic analysis of right-sided colon cancer, left-sided colon cancer and rectal cancer reveals distinct mutational profiles. Mol Cancer. 2018. 17(1): 177.

[38] Li Y, Liu W, Pei Q, Zhao L, Güngör C, Zhu H, Song X, Li C, Zhou Z, Xu Y, Wang D, Tan F, Yang P, Pei H. Predicting pathological complete response by comparing MRI-based radiomics pre- and postneoadjuvant radiotherapy for locally advanced rectal cancer. Cancer Med. 2019. 8(17): 7244-7252.

[39] de Cheveigné A, Nelken I. Filters: When, Why, and How (Not) to Use Them. Neuron. 2019. 102(2): 280-293.

[40] Liang C, Huang Y, He L, Chen X, Ma Z, Dong D, Tian J, Liang C, Liu Z. The development and validation of a CT-based radiomics signature for the preoperative discrimination of stage I-II and stage III-IV colorectal cancer. Oncotarget. 2016. 7(21): 31401-12.

[41] Cui Y, Yang X, Shi Z, Yang Z, Du X, Zhao Z, Cheng X. Radiomics analysis of multiparametric MRI for prediction of pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Eur Radiol. 2019. 29(3): 1211-1220.

[42] Yi X, Pei Q, Zhang Y, Zhu H, Wang Z, Chen C, Li Q, Long X, Tan F, Zhou Z, Liu W, Li C, Zhou Y, Song X, Li Y, Liao W, Li X, Sun L, Pei H, Zee C, Chen BT. MRI-Based Radiomics Predicts Tumor Response to Neoadjuvant Chemoradiotherapy in Locally Advanced Rectal Cancer. Front Oncol. 2019. 9: 552.

[43] Huang YQ, Liang CH, He L, Tian J, Liang CS, Chen X, Ma ZL, Liu ZY. Development and Validation of a Radiomics Nomogram for Preoperative Prediction of Lymph Node Metastasis in Colorectal Cancer. J Clin Oncol. 2016. 34(18): 2157-64.

[44] Zhao X, Xie P, Wang M, Li W, Pickhardt PJ, Xia W, Xiong F, Zhang R, Xie Y, Jian J, Bai H, Ni C, Gu J, Yu T, Tang Y, Gao X, Meng X. Deep learning-based fully automated detection and segmentation of lymph nodes on multiparametric-mri for rectal cancer: A multicentre study. EBioMedicine. 2020. 56: 102780.

[45] Qu A, Yang Y, Zhang X, Wang W, Liu Y, Zheng G, Du L, Wang C. Development of a preoperative prediction nomogram for lymph node metastasis in colorectal cancer based on a novel serum miRNA signature and CT scans. EBioMedicine. 2018. 37: 125-133.

[46] Bibault JE, Giraud P, Housset M, Durdux C, Taieb J, Berger A, Coriat R, Chaussade S, Dousset B, Nordlinger B, Burgun A. Deep Learning and Radiomics predict complete response after neo-adjuvant chemoradiation for locally advanced rectal cancer. Sci Rep. 2018. 8(1): 12611.

**Figure Legend**

**Figure.1** **The diagram of workflow in this study**.

**Figure.2** **Tumor segmentation.** Four cases of tumor segmentation for portal venous-phase contrast-enhanced CT images and T2-weighted-MRI images. Two patients achieving pCR (a, c) and two non-pCR patients (e, g) were demonstrated respectively. Segmentation of ROI for the four cases were shown (b, d, f, h).

**Figure.3** **The distribution of rad-scores.** The rad‐score for each patient in the primary cohort (a) and the validation cohort (b), respectively.

**Figure.4** **Model construction.** Process of model training in LASSO logistic regression model (a, b), gradient boosting model (c), and random forest model (d). (a) Selection of the tuning parameter (λ) for the LASSO model via ten-fold cross-validation according to the criteria of AUC value; (b) LASSO coefficient profiles of the selected radiomic features with non-zero coefficients at the optimal λ; (b) Selection of the best RF model via cross-validation according to the criteria of AUC value; (d) Selection of the best GBM model via cross-validation according to the criteria of AUC value. For a, c, d, the models with the highest AUCs were outlined.

**Figure.5** **Performance of CT-based models.** The ROC curves of the radiomics models using different methods in the primary cohort (a) and validation cohort (b), respectively. The decision curve analysis for the multivariable logistic radiomics model(c) showed that if the threshold probability is between 0 and 1, using the radiomics model to predict pCR adds more benefit than treating either all or no patients. The y-axis measures the net benefit. The x-axis represents the threshold probability. The red line represents the radiomics model. The grey line represents the assumption that all patients achieved pCR. The black line represents the hypothesis that no patients achieved pCR.

**Figure.6** **Performance of the integrated model.** (a) The Mixed rad‐score for each patient in the subcohort; (b) Comparison of CT-based model, MRI-based model, and the integrated model via resampling.