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Enhancing A Radiomics-Based Pathological Response Prediction for Locally Advanced Rectum Cancer

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1. Abstract

1.1. Aims: This study aims to further enhance a validated radiomics-based model for predicting pathologic complete response (pCR) after chemo-radiotherapy (CRT) in LARCs for use in the clinical practice.

1.2. Methods: A generalized linear model (GLM) to predict pCR in LARC patients previously trained in Europe and validated with external inter-continental cohort (59 patients) was first examined with further 88 intercontinental patient datasets to assess its reproducibility; new radiomics and clinical features, and validation methods were investigated. The patients were divided into training group (75%) and validation group (25%) according to their demographic. The least absolute shrinkage and selection operator (LASSO) logistic regression was used to reduce the dimensionality of the extracted features of the training group and screen the optimal ones; the performance of the reference GLM and enhanced models was compared through the area under the curve (AUC) of the receiver operating characteristics (ROC).

1.3. Results: The value of AUC of the reference model was 0.831 (95% CI, 0.701 - 0.961), and 0.828 (95% CI, 0.700 - 0.956) in the original and new validation cohorts, respectively, showing a reproducibility in the applicability of the original model. Nine features were found to be significant with LASSO model and added in the new model. The AUC of the enhanced model of 0.926 (95% CI, 0.859-0.993) for training, and 0.926 (95% CI, 0.767-1.00) for the validation group show better performance than the reference model.

1.4. Conclusion: GLM model show a good reproducibility in predicting pCR in LARC; the enhanced model has the potential to improve prediction accuracy and may be a candidate in clinical practice.

2. Introduction

For locally advanced rectal cancer (LARC), the standard-of-care treatment is preoperative concurrent chemoradiation treatment (CRT) followed by total mesorectal excision (TME). While TME remains the gold standard it is associated with significant morbidity and long-term effects on anorectal, urinary, and sexual function [1, 2]. Moreover, despite the consensus on this treatment schedule, the response of these tumors is heterogeneous, with approximately 20% of patients showing a pathologic complete response (pCR) [3,4], which might be indicative of a prognostically favorable biological tumor profile with less propensity for local or distant recurrence and improved survival [5]. In those who achieve a pCR, some investigators have questioned the use of TME surgery, and investigated the appropriateness of proceeding with a partial resection, or even omitting surgery while undertaking intensive follow-up [6, 7]. It is critical to be able to early identify those patients who will have a complete

clinical response to provide physicians with accurate information for making decisions about a personalized treatment path.

Recently, radiomics has emerged as a viable and powerful tool for diagnostic and prognostic purpose [8]. The term radiomics refers to the extraction and analysis of features from medical images acquired by proton emission tomography, computed tomography, magnetic resonance (MR), etc., to build descriptive, diagnostic, or predictive models. These medical images effectively carry an immense source of potential data for decoding tumor phenotypes[9]. The strength of radiomics lies in the wide use and non-invasiveness of medical imaging in clinical routine. The translation of radiomics analysis into standard cancer care to support treatment decision-making involves the development of prediction models integrating clinical information that can assess the risk of specific tumor outcomes [8, 9]. Many studies have gone in this direction by developing predictive models from routine imaging; Wang et al. [10] used contrasted CT-based radiomics of the rectum and mesorectum for the prediction of neoadjuvant rectal score and survival outcomes in LARC; Nie et al [11]. Using MRI-based radiomics set up a predictive model for pCR in LARC obtaining values for the AUC ranging from 0.53 to 0.73; similarly Li et al [12]. Achieved a value of the AUC of 0.87.

In the case of rectal cancer, the MRI acquired at diagnosis, during and after treatment, are the basis for the study of predictive models of treatment outcome. The identification of features to be extracted is of crucial importance for the development of the objective model of radiomics. The number of features potentially extractable from an image is high, however not all of them have sufficient robustness to sources of variability [8]. It is therefore necessary to make a rigorous selection to ensure the efficiency of the model and make it applicable to patients not yet evaluated. Once created the model it is necessary to verify the validity by evaluating the predictive ability on sets of extraneous data to the training set used in phase of modeling. The performance of the model is measured through the area under the curve (AUC) of the receiver operating characteristics (ROC), which takes values between 0 and 1. The ROC is obtained by evaluating the ratio between true positive rate (TPR) and false positive rate (FPR) of the model. By calculating the area covered by the ROC, it is possible to obtain an index of the sensitivity and specificity of the predictive model.

This study aims to include in the clinical practice a prediction model for accurate prediction of response to chemoradiation in patients with LARC to help the radiation oncologist in making decisions on treatment strategies. First, we assessed a previous reported two-features radiomics prediction model developed in Europe [13, 14] on a new cohort of patients. Moreover, we investigated the addition of radiomics features and validation methods to further enhance the accurate prediction of response to chemoradiation in patients with LARC.

4. Material and Methods

4.1. Reference Model

A generalized linear model (GLM) [15] to predict pCR in LARC patients built using a single center training set of 162 patients and 2 external validation sets of 34 and 25 patients, respectively provided by other European centers was used as reference predictive model in this study. The model is magnetic resonance (MR) vendor independent and is based on 4 covariates: clinical T and N staging and 2 radiomics features extracted from staging 1.5 T MRI. The considered binary outcome was pCR achievement. Discrimination performance of the model, evaluated by AUC of the ROC showed an AUC of 0.73 (95% CI 0.65-0.82) in the training cohort and 0.75 (95% CI 0.61-0.88) in the testing cohort. Successively, the model was validated with an inter-continental cohort of 59 patients from our Institute showing a AUC of 0.831 (95% CI, 0.701 - 0.961) [16].

4.2. Patients

A total of 88 patients affected by pathologically proven locally advanced rectal adenocarcinoma, clinical stage T3-4N0 or T1-4N1-2 and treated in Sichuan Cancer Hospital & Institute between March 2017 and December 2020, were enrolled in this retrospective study. This study was approved by the Ethics Committee of Sichuan Cancer Hospital (approval number SCCHEC-02-2020-008). The need for informed written patient consent was waived due to the retrospective nature of this study, nevertheless the patients gave oral consent to the use of their anonymized data for research purposes.

Patients with distant metastases, prior chemotherapy, or radiotherapy for rectal cancer, previous or concurrent malignancies, and known allergies to intravenous contrast agents or other contraindications for MR imaging (MRI) acquisition were excluded. All patients received preoperative chemoradiation followed by TME surgery and MR examinations one week before the chemoradiation. The treatment protocol and timeline were as follows: after an initial cycle of chemotherapy CapOx lasting about three weeks and foreseeing capecitabine 1000 mg/m2 at d1-14 concurrently with oxaliplatinum 130 mg/m2 d1, patients followed two different treatment schedules before TME. The first treatment scheme involved a one-week short course of external beam radiotherapy (EBRT, 25 Gy in 5 fractions of 5 Gy per fraction) followed directly after one-week gap to TME; the second treatment scheme involved neoadjuvant CRT (nCRT) administering EBRT for 5-6 weeks (50.4 Gy in 28 fractions of 1.8 Gy each) concurrently with chemotherapy (Capecitabine 825 mg/m2 die), at the end of which two more cycle of CapOx, then TME after a recovery interval of 2 weeks. TME was performed by either anterior resection or abdominoperineal resection. The pathologic staging served as the reference standard and was determined according to the TNM classification system recommended by the American Joint Committee on Cancer (AJCC), 7th ed., 2012 [17]. The resection specimens were evaluated by an experienced pathologist blinded to the MRI data.

Response to nCRT was determined by histopathological examination of surgically resected specimens: tumour responses were classified using tumor regression grade (TRG) according to Mandard et al. [18] as pCR (TRG = 1), or non-responder (TRG > 1).

4.3. Magnetic Resonance Imaging

All patients were scanned in our Institute with a 3.0 Tesla MR (Siemens Skyra, Siemens Medical Systems) scanner, using a phased-array body coil one week before the start of chemoradiation with fixed image protocols. No special bowel preparation was performed. The MR machine underwent quality assurance check monthly by the medical physics department with particular attention to the image's quality controls. The scanning protocol followed by the patient and used for this study consists of an axial T2-weighted fast spin echo sequence, with 2,840/131 (ms) as the ratio of repetition time to echo time (TR/TE), image resolution 0.49 x 0.49 x 4 mm, pixel spacing 0.625 mm, slice spacing 3 mm and slice thickness 3 mm.

4.4. Features Extraction

All MR images were reviewed in MIMMaestro workstation (MIM software Inc, Cleveland, OH) by a single experienced rectal MRI radiologist who delineate the gross tumor volume (GTV) following the guidelines defined in ICRU n.83 [19]. The segmentation process was performed manually and the radiomics analysis was focused on the entire volume. The DICOM files containing the MR images and the corresponding radiotherapy (RT) Structure files were imported in Moddicom, an open-source R (R Core Team, Vienna, Austria) statistical software package [20] . Images were pre-processed with the Laplacian of Gaussian (LoG) convolution kernel filter; to decrease the noise of the high-frequency MRI signal and reduce the impact of large signal variations, the size of the standard deviation (σ) in the LOG filter was scanned from 0.1 to 1.0 with a step-size of 0.05. To search for potential GTV features related to outcome prediction five feature groups were extracted, including statistical, morphological, grey-level co-occurrence matrix (GLCM), grey-level run length matrix (GLRLM), grey-level size zone matrix (GLSZM). In addition, three potential clinical factors, i.e., clinical T-stage (cT), clinical N-stage (cN) and age, were also considered in the statistical analysis.

4.5. Statistical Analysis and Model building

Among all features initially extracted and the clinical factors, the Mann-Whitney test was used to skim the number to only features significant for pCR. Moreover, to further reduce the number of final feature predictors and avoid multicollinearity between them, the binary logistic regression model LASSO (least absolute shrinkage and selection operator) was used to search an optimal subset of features and establish a linear relationship between them and the pCR. By increasing the lambda parameters incorporated in the LASSO model, more non-zero coefficients of the variables (features) were set to 0, so fewer variables would be chosen in the logistic regression model. The variation of the subset of features with their corresponding coefficients in the model changes the AUC of the ROC. With 5-fold cross-validation, the best lambda counterpart with the highest AUC was selected. The 95% confidence interval of AUC of each ROC were computed using bootstrap method with 1000 resamplings.

5. Results

5.1. Patient Characteristics

In this study, we enrolled 88 LARC patients who underwent standard CRT, including 12 (13.6%) responders and 76 (86.4%) non responders to enhance the performance of the reference model. Patient tumors characteristics and outcomes are reported in Table 1. There were no significant differences in clinical variables between the original cohort used to validate the reference model and the new cohort used to set up the enhanced model.

Table 1. Patient and tumour characteristics, clinical data, and response outcome.

	Original cohort	**New cohort**	***p* value**
Number	59	88	
Age			0.387
Years, median (range)	56.0 (34.0-74.0)	55.5 (29.0-73-0)	
Sex – no. (%)			0.565
Male	47 (79.7)	60 (70.6)	
Female	12 (20.3)	25 (29.4)	
Tumor stage – no. (%)			
cT stage			0.239
T2	6(10.2)	2 (2.3)	
T3	34 (57.6)	61 (69.3)	
T4	19 (32.2)	25 (28.4)	
cN stage			0.365
N0	25 (42.4)	29(32.9)	
N1	24 (40.7)	21(23.9)	
N2	10(16.9)	38 (43.2)	
Interval between MRI and start CRT			
Days, median (range)	14 (4-50)	13 (4-35)	
Interval between end CRT and surgery			

RT Short Course: days, median (range)	10 (8-15)	9(5-15)	
RT Long Course: days, median (range)	59(30-82)	67(30-108)	
RT Course			
Short (5fr x 5Gy)- no. (%)	19 (32.2)	10 (11.4)	
Long (28fr x 1.8Gy)- no. (%)	39 (67.8)	78 (88.6)	
eMR scanner Strength			
1.5 T no (%)	32 (54.2)		
3.0 T no (%)	27 (45.8)	88 (100.0)	
TRG			
1 – no. (%)	10 (16.9)	12 (13.6)	
2-5 – no. (%)	49 (83.1)	76 (86.4)	

^ In the long radiotherapy course, two more chemotherapy cycles were scheduled at the end of the radiotherapy before surgery.

5.2. Feature Selection of Radiomic Signature

A total of 1643 features were obtained from the LoG filtered T2-weighted MR images. Sixty features were found significant for pCR in the Mann-Whitney test. In the LASSO model, λ was chosen by 5-fold cross-validation, and log(λ) of -3.13 was the optimal subset for eight radiomics features i.e surface to volume ratio, sum variance, cluster tendency, entropy, high grey level run emphasis, sum entropy, high grey level run emphasis 1, and mean intensity with Log filters of variant sigma, and one clinical feature (age). Features adopted are listed in Table 2, at which these potential predictors were selected with a nonzero coefficient of the LASSO logistic regression model. Figure 1 highlights how the number of variables contained in the model varies with the lambda parameter.

The radiomics signature score was assessed for each patient based on the nine features. Waterfall plots showed the rad score for individuals in the training cohort (Figure 2A) and validation cohort (Figure 2B). There was a significant difference in rad score between pCR and non-pCR group in both the training ($p < 0.001$) and the validation cohort ($p < 0.003$).

Table 2. The coefficient, and sigma of LoG filter for the eight features adopted in the enhanced prediction model.

Feature name	Sigma of LoG filter	Coefficient
Sum Entropy	0.65	1.45E0
Surface to Volume ratio	0.7	5.67E-01
Entropy	0.5	-1.46E-01
Age	-	-7.7E-03
High Grey Level Run Emphasis	0.6	1.27E-03
Sum Variance	0.65	1.26E-03
Mean Intensity	0.65	-4.57E-04
High Grey Level Run Emphasis 1	0.6	3.16E-07
Cluster Tendency	0.65	2.37E-17

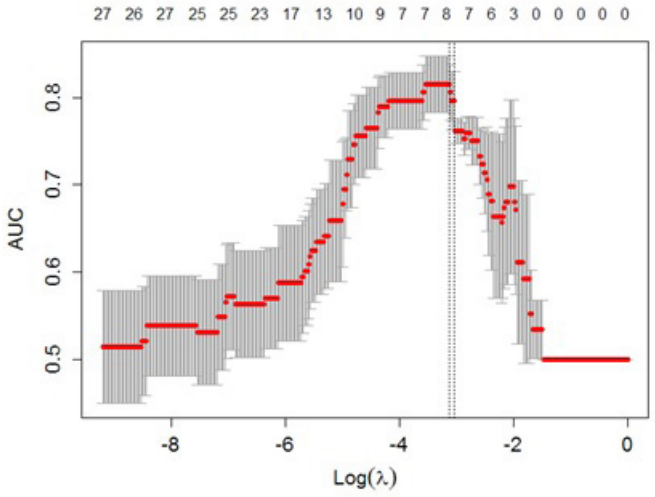

Figure 1: Selecting the optimal lambda value for the enhanced LASSO model.

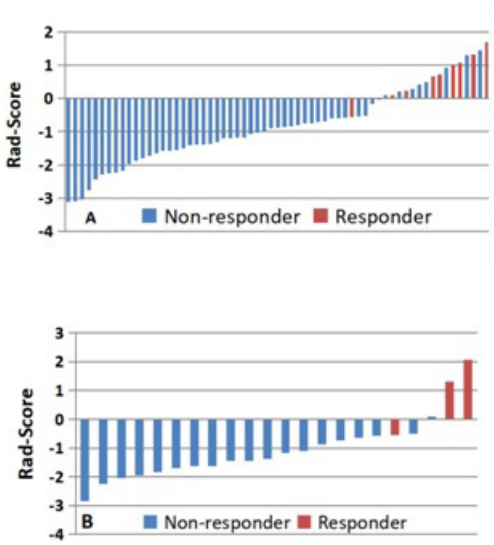

Figure 2. The radiomics score of the enhanced model for patients in (A) the training cohort and (B) the validation cohort.

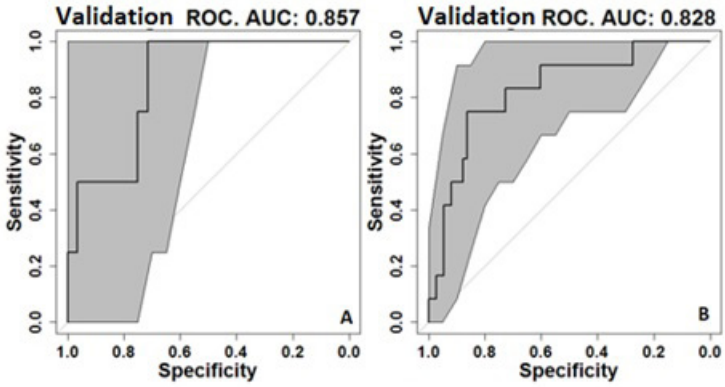

Figure 3. ROC curve of the reference model for the original (A) and new (B) validation cohort of patients.

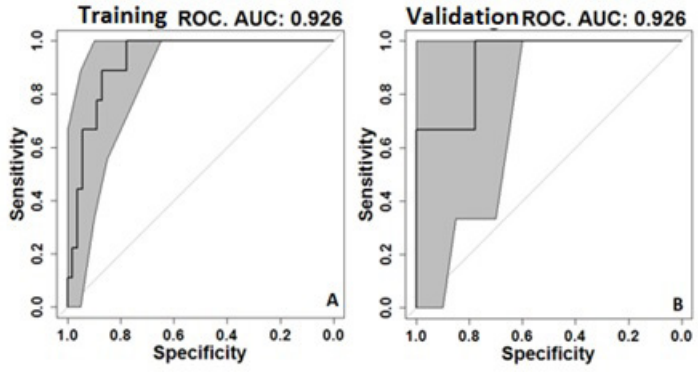

Figure 4. ROC curves of the enhanced model for the training (A) and validation (B) group of the new cohort of patients.

5.2. Enhanced Model

The AUC value of the ROC curves of the reference model for the original cohort and new cohort of patients are shown in Figure 3; the AUC of 0.831 (95% CI, 0.701-0.961), and 0.828 (95% CI, 0.700-0.956) in the original and new validation cohorts, respectively, showed reproducibility in the applicability of the original model; whereas the AUC value of the ROC curves of the enhanced model portrayed in Figure 4 is 0.926 (95% CI, 0.859-0.993) for the training and 0.926 (95% CI, 0.767-1.00) for the validation group.

6. Discussion

At present, pathological evaluation of the surgical specimen is the only reliable surrogate marker that correlates with long-term oncological outcomes. However, such data are only available after completion of all preoperative treatments and surgery and cannot be used to guide the therapeutic approach. Therefore, the development of non-invasive biomarkers with the capacity to provide early prediction is essential. Such biomarkers would help to identify patients who are less likely to benefit from current therapies as they are more likely to have a pCR. Therefore, individually adapted surgical strategies could be considered for such patients, or they could be referred to alternative treatments or intensive follow-up schemes.

Di Napoli et al. [15] established a GLM to predict pathological pCR after CRT for LARC patients based on two radiomic features and two clinical parameters trained in Europe and validated with external inter-continental cohort, including and a cohort of 59 patients coming from our Institute [16 -21]. Findings from this study confirm the performance and reproducibility of the original GLM. Furthermore, this retrospective study investigated how to enhance the prediction of pCR in patients with LARC of the GLM to evaluate its use in the clinical routine of our department as decision support for the oncologist. For this purpose, patients following our institute's standard protocols for both magnetic resonance imaging and treatment pathway were retrospectively enrolled.

In our research, we still hypothesize that radiomic features are important prognostic factors for risk assessment of specific rectal cancer outcomes. In this regard, the model was reworked by extracting much more features from a cohort of patients from our institution having MRI imaging with uniform characteristics and protocols, as well as the type of well-defined treatment course. Considering finding the most significant ones from a large number of initially extracted features, we adopted the LASSO model in this study. Compared to the previously developed GLM model, L1 regularization was also added in the cost function of LASSO, which enables to reduce of the dimensionality of radiomic features and avoid multilinearity. Finally, eight radiomics features and one clinical factor were selected after the regression coefficient of other features were penalized to zero. Comparing those predictors(features) in previous GLM and current LASSO, only entropy of GTV is shared by both predictive models while other predictors are different. The finding of AUC of 0.926 indicates that LASSO indeed has an enhanced predictive performance compared to GLM.

To get a reliable and reproducible result in radiomics study, it is essential to guarantee the repeatability of features extraction process. Radiomics in MR can return issues that depend on typical absolute value variations of MR signal recorded in numerical format inside

DICOM files [21] changing according to patients, sequences, acquisition parameters, or simply time. Furthermore, MR can be affected by several patterns of noise that can interfere with quantitative analysis of signal values [22] and heterogeneity- of MR numerical data is a well-known issue for the analysis; moreover, considering that geometrical distortions are quite common in MRI [23], we cannot exclude that this has an impact on feature extraction. The rationale for optimizing a model already validated in a cohort of patients from our hospital lies in the fact that the cohort of patients is representative of the patient population coming from our hospital.

Many radiomics studies are relying on retrospective datasets, in which individual image acquisition parameters can be different. These different settings can influence the quality and reliability of the extracted radiomics features [24], for the commonly used imaging modalities. Zhao et al [25]. Conducted a study and concluded that the repeatability of features[26] derived from scans with the same imaging setting was good, however only 19% of the features were repeatable when different settings were used. Fave et al [27][27]. Found that radiomics features may be reliable as long as the imaging protocol is consistent and relative differences are used.

The application of MR for radiomics has always been considered affected by many issues due to the intrinsic difficulty in generalizing the analysis of the signal in MR images because of the problem of normalization and regularization of MR images [28]. The results obtained suggest that the extracted features discriminate better between pCR and non-pCR patients reaching a statistical significance even one order of magnitude higher than the initial radiomics analysis performed on a more heterogeneous sample. This is also reflected in the better performance of the improved model, achieving improved AUC curve specificity values.

Manual delineation of the gross tumour volume is a standard clinical routine in the treatment planning process for patients receiving radiotherapy, but for other interventions, this is not frequently performed. Manual delineation is a straightforward solution but is also susceptible to inter-observer variability. These differences can influence radiomics features extracted from the delineated volumes. Van Velden et al [29. Investigated the influence of reconstruction and delineation on the repeatability of radiomics features in NSCLC patients on PET-CT imaging, and concluded that 24% of the features were susceptible to the delineation method. Even if radiomics on MRI has not been investigated as extensively as on CT and PET scans, its potential value to discriminate outcomes has been shown by Gnep et al . [30] for prostate treatments.

The present study has some limitations. First, the sample size is still limited compared with the relatively large number of predictors. Moreover, the conventional logistic regression analysis has not the capacity to model complex relationships between independent and predictor variables, allowing the inclusion of many variables. The training and validation were performed on the same set of patient data. To minimize the bias, 5-fold cross-validation was used [31]. Furthermore, a reliable predictive or prognostic power is necessary if implemented in the clinical routine for individual decision-making.

7. Conclusion

Through a systematic analysis of MR imaging features, we were able to build a model with improved predictive value. The results are encouraging, suggesting the abundance of radiomics imaging should be further explored to help tailor the treatment into the era of personalized medicine. Previously GLM model show good reproducibility in predicting pCR to CRT in LARC; the enhanced LASSO model developed in this study has the potential to improve prediction accuracy.

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