Development and Validation of Radiomics Signatures to Predict KRAS Mutation Status Based on Triphasic Enhanced Computed Tomography in Patients with Colorectal Cancer

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Abstract

Purpose: In this study, we used computed tomography (CT)-based radiomics signatures to predict the mutation status of *KRAS* in colorectal cancer (CRC) patients.

Methods: This study involved 447 patients who underwent *KRAS* mutation testing and preoperative triphasic enhanced CT. They were categorised into training (n = 313) and validation cohorts (n = 134) in the ratio 7:3. Radiomics features were extracted from CT imaging. The Boruta algorithm was used to retain the features closely associated with *KRAS* mutation. Multivariate logistic regression was used to develop radiomics, clinical, and combined clinical-radiomics models for *KRAS* mutation. The receiver operating characteristic curves were used to evaluate the predictive performance and clinical usefulness of each model.

Results: Fourteen radiomics features were retained as the final signatures for predicting *KRAS* mutations. Delayed phase models showed superior predictive performance compared to arterial phases models or venous phase models. The clinical-radiomics fusion model showed excellent performance, with an AUC, sensitivity and specificity were 0.772, 0.792 and 0.646 in the training cohort, while 0.755, 0.724 and 0.684 in the validation cohort, respectively.

Conclusions: The clinical-radiomics fusion model can be used as a potential imaging marker for preoperative detection of *KRAS* mutation status.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide and causes almost 881,000 deaths every year¹. The incidence of colorectal cancer is approximately 3-fold higher in developed countries than in developing countries. However, as the developing countries become richer, increasing trends is likely to be seen in these countries². Kirsten rat sarcoma (*KRAS*) viral oncogene homologue is a G protein, which occurs in 40-50% cases of CRCs. Following the mutation in *KRAS* gene, the mutant protein activates downstream mitogen-activated protein kinase (MAPK) pathway, subsequently leading to uncontrolled cell proliferation and malignancy³. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines have explicitly indicated that CRC patients with *KRAS* mutations are resistant to anti-EGFR monoclonal antibody therapy⁴. Therefore, *KRAS* mutation testing is crucial for individualised and effective treatment of CRC.

Generally, pathologic specimens obtained via invasive procedures such as colonoscopy or surgery are usually required for the identification of *KRAS* mutation status. However, the presence of extensive heterogeneity in CRC archival samples represents a major limitation of the histological approach⁵. Additionally, postoperative tissue specimens might not be obtained for testing from patients with metastatic CRC specimens⁶. Furthermore, biopsy testing might not be an effective approach to determine the mutational status of *KRAS* due to poor DNA quality⁷. Therefore, it is necessary to develop a non-invasive and easy-to-use method to identify *KRAS* mutation status.

Several studies have demonstrated the use of medical imaging technology, such as fluorine-18 fludeoxyglucose (18F-FDG) positron emission tomography (PET) and magnetic resonance imaging, in the prediction of *KRAS* status^{8,9}. However, these studies involved small sample sizes and lacked validation. Radiomics provides a variety of parameters for quantitative analysis, and these parameters have been widely used in cancer diagnosis, classification, and prediction¹⁰. A previous study demonstrated a significant correlation between a CT-based radiomics signature and *KRAS/NRAS/BRAF* mutations in CRC patients¹¹. However, this study involved a small sample size and was only performed in the venous phase. Moreover, the superiority of venous phase as compared to arterial or delay phases in the prediction of *KRAS* mutation status in CRC patients remains to be confirmed. The aim of this study was to investigate whether a CT-based radiomics signature could identify *KRAS* mutation status in CRC patients and whether the venous phase is superior to arterial and delay phases in the prediction of *KRAS* mutation status in CRC patients.

Results

Clinical Characteristics

This study involved a total of 447 CRC patients in the final analysis, including 263 men (58.8%) and 184 women (41.2%), with an average age of 58.93 ± 12.85 years. Among the 447 patients, 207 patients contained mutated *KRAS* and 240 patients contained wild-type *KRAS*. We used stratified sampling to categorise the study cohort into a training cohort (n = 313) and a validation cohort (n = 134) in the ratio of 7:3. The training cohort and validation cohort were used for model building and internal validation, respectively. Patient and tumor characteristics in the training cohort are listed in Table 1.

Table 1
Demographic and Clinical Characteristics of and CT Findings for CRC (mean $\pm$ SD or no. (%)).

Characteristics ¹	Training cohort (n=313)		
	KRAS WT (n=164)	KRAS MT (n=149)	P value ²
Age (years)	57.58 $\pm$ 12.81	60.50 $\pm$ 12.75	0.023
Gender Female	63 (38.4%)	66 (44.3%)	0.291
Male	101 (61.6%)	83 (55.7%)	
Tumor Location Left	115 (70.1%)	100 (67.1%)	0.567
Right	49 (29.9%)	49 (32.9%)	
CEA level Normal	101 (61.6%)	72 (48.3%)	0.018
Abnormal	63 (38.4%)	77 (51.7%)	
CA125 level Normal	150 (91.5%)	135 (90.6%)	0.790
Abnormal	14 (8.5%)	14 (9.4%)	
CA199 level Normal	120 (73.2%)	90 (60.4%)	0.016
Abnormal	44 (26.8%)	59 (39.6%)	
cT stage T1	2 (1.2%)	9 (6.0%)	0.023
T2	21 (12.8%)	29 (19.5%)	
T3	107 (65.2%)	90 (60.4%)	
T4	34 (20.7%)	21 (14.1%)	
cN stage N0	100 (61.0%)	81 (54.4%)	0.281
N1	37 (22.6%)	33 (22.1%)	
N2	27 (16.5%)	35 (23.5%)	
Maximum diameter (mm)	22.42 $\pm$ 9.95	21.85 $\pm$ 8.88	0.825
¹ Continuous variables were expressed as mean $\pm$ standard deviation; Classification variables were represented by no. (%);			
² Student's t-test or Mann-Whitney U test was used to compare continuous variables; Chi-squared test or Fisher's exact test was used to compare categorical variables.			
Abbreviations: WT, wild type; MT, mutated type			

Predictive Performance of the Clinical Model

In the training cohort, the clinical characteristics age, CEA, CA199, and cT stage were found to be significantly different statistically ($P < 0.05$), and the other characteristics not significantly different ($P > 0.05$) between mutated *KRAS* and wild-type *KRAS* groups (Table 1). Therefore, after multivariate analyses, clinical characteristics including age, CEA and cT stage were selected as independent predictors of *KRAS* mutation and enrolled into clinical model. The clinical model showed lower performance in predicting *KRAS* mutation both in the training cohort and the validation cohort, with the AUC being 0.654 (95%CI, 0.593-0.714) in the training cohort and 0.575 (95%CI, 0.478-0.672) in the validation cohort (Table 2). The accuracy, sensitivity, and specificity were 0.617, 0.664, and 0.573 (training cohort) and 0.552, 0.552, and 0.553 (validation cohort), respectively.

Table 2. Predictive performance of different models in training and validation cohorts.

The DCA curves for the clinical model, radiomics models, and clinical-radiomics model is presented in Figure 5A-B. The combined clinical-radiomics model achieved more clinical utility in predicting the *KRAS* mutation than the clinical model and other radiomics models. The DCA curves of the clinical-radiomics model demonstrated that when the threshold probability of a patient or doctor ranged between 20% and 65%, the use of the clinical-radiomics nomogram adds greater benefit for *KRAS* mutation prediction than the treat-all-patients scheme or the treat-none scheme in training and validation cohorts.

Discussion

In this study, clinical, radiomics, and clinical-radiomics model were developed for the preoperative prediction of *KRAS* mutations. We answered a question that the DP model had a higher outstanding performance than the AP or VP models. Additionally, the clinical-radiomics model showed higher predictive performance than the clinical model or radiomics model alone. The calibration curve and decision curve of clinical-radiomics model showed excellent model stability and actual benefit.

KRAS mutations can lead to continuous activation of the EGF/RAS/RAF/ERK signalling pathway without the regulation of EGFR, gradually leading to increased cell proliferation and decreased apoptosis^{12–14}. Colorectal cancer with *KRAS* mutation is a negative marker for anti-EGFR targeted drugs¹⁵. Numerous studies^{16,17} have used ¹⁸F-FDG PET/CT to investigate the association between *KRAS* mutation and ¹⁸F-FDG uptake and demonstrated that cells with *KRAS* mutation had higher ¹⁸F-FDG uptake than those with wild-type *KRAS*. However, there was no correlation observed between them according to a study by Riklis et al.¹⁸. The major clinical use of PET/CT in CRC is to detect potentially curable metastases. Yang et al.¹¹ proposed a CT-based radiomics model to identify *KRAS/NRAS/BRAF* mutation in CRC and found a relatively high predictive performance. However, this study defined the positive group based on mutations in any of *KRAS/NRAS/BRAF*, which would complicate the clinical application.

During the image preprocessing stage, the LoG filter and wavelet filter were applied to process the original image. The LoG filter can smoothen the image and improve the efficiency of capturing phenotypic features related to tumor heterogeneity¹⁹. The wavelet filter could disassemble the frequency signal of the image to extract edges and substantial features of tumor more effectively. This study finally screened out 25 radiomics features as the radiomics signatures of the AP, VP, DP, and triphasic enhanced combined phase. The features with wavelet filtering accounted for 52% (13/25) of the total features. This shows that the wavelet filter is very important for extracting features related to *KRAS* mutations status, while the features with LoG filters are not used as radiomics signatures for predicting *KRAS* mutations, indicating that the features extracted from the LoG filter images were weakly correlated with *KRAS* mutations.

Multivariable regression analysis combined with the radiomics signatures of triphasic enhanced phases, 11 radiomics features were retained as key features for identifying *KRAS* mutation status (Table 3), including 5 texture features: A_wavelet.HHH_glszm_GrayLevelNonUniformityNormalized, A_wavelet.LLL_glcM_MCC, D_wavelet.HLL_glcM_Idn, D_wavelet.HLL_gldm_SmallDendenceLowGrayLevelEmphasis, D_wavelet.LLL_glcM_Idn. Texture features are microscopic descriptions of tumors, reflecting the interaction between adjacent pixels, and reflect tumor heterogeneity²⁰. These features are not easily identified by the human visual system and cannot be interpreted as having a clear meaning. Previous studies have shown that texture features may be associated with tumor microenvironment reflecting tumor heterogeneity, presence of hypoxia or angiogenesis^{21–23}. A studies²⁴ found that *KRAS* mutations were associated with higher texture characteristic values (Gskewness and SDs), indicating that mutated *KRAS* had more tumor heterogeneity than wild-type *KRAS*. The radiomics score values of texture features (A_wavelet.LLL_glcM_MCC, D_wavelet.HLL_gldm_SmallDendenceLowGrayLevelEmphasis) in the *KRAS* mutation group was higher than that in the wild group, which suggests that tumor tissue is more tumor heterogeneous in the ROI range. Combined with the results of this study and other studies, it is shown that texture features can be used as noninvasive imaging markers for predicting *KRAS* mutations status.

In addition, five morphological features (A_original_shape_Elongation, V_original_shape_Maximum2DDiameterSlice, D_original_shape_Elongation, D_original_shape_Maximum3DDiameter, D_original_shape_Sphericity) were also closely correlated with *KRAS* mutations, suggesting that the morphological characteristics of mutant *KRAS* and wild-type *KRAS* tumor were significantly different, which was consistent with previous literature. A study¹⁹ found morphological features (Elongation and flatness) were closely associated with *KRAS* mutations in rectal cancer. A study⁹ explored the correlation between *KRAS* mutations in rectal cancer and tumor morphology on magnetic resonance images, the study found that the average axial/longitudinal ratio of *KRAS* mutations rectal cancer was greater than that of *KRAS* wild-type tumor (0.46 ± 0.29 vs. 0.36 ± 0.20 , $P = 0.009$).

Among the triphasic enhanced phase models of *KRAS* mutation prediction in the training cohort, the DP model showed the highest performance, with an AUC value of 0.752, followed by 0.711 in the AP model and 0.692 in VP model. To our knowledge, this is the first time that the triphasic enhanced CT radiomics has been used in *KRAS* mutation prediction. Although the VP is the most commonly used phase in gastrointestinal radiomics research, contrary to the results assumed in this study, the enhancement phase with the best predictive performance was the DP rather than the VP. One reason for the high predictive performance of the DP model is the possibility of high content and uniform distribution of contrast agent in the DP lesions²⁵. Another reason for the high predictive performance of the DP model may be that the ROI range of tumors in the DP images is larger than that in the AP and VP²⁵.

In terms of clinical characteristics, Age, CEA and CA199 were independent predictors for *KRAS* mutation. In this study, *KRAS* mutations patients were older than *KRAS* wild-type patients, and the difference was statistically significant ($P < 0.05$), this result is consistent with the previous literature²⁶. CEA and CA199 were significantly higher for the mutated *KRAS* group than for the wild-type *KRAS* group in our study. Our finding is in line with those from previous studies^{27,28}. Both *KRAS* mutation and elevated serum levels of CEA and CA199 are associated with more aggressive biological behaviour in CRC patients^{29–31}. A correlation between *KRAS* mutations and higher CEA and CA199 levels suggests that genetic alterations may have independent influences on CRC development, thus resulting in increased tumor biomarkers³².

Triphasic enhanced CT is often conducted in gastrointestinal tumors CT examination. The AP is used for tumor detection, the VP is used to differentiate the tumor from adjacent organs, and the DP is used to determine the depth of tumor invasion³³. As for radiation dose, the average DLP value of triphasic enhanced scans was 1917.52 ± 152.31 mGy cm, which is slightly higher than the diagnostic reference level (DRL) for adults (1490 mGy cm) published by

China's National Health Industry standard (WS/T 637-2018)³⁴. Application of new techniques such as multi-model iterative reconstruction technology could effectively reduce the radiation dose in clinical practise³⁵.

Our study should be interpreted after considering several limitations. First, 269 patients were excluded because they did not meet the inclusion and exclusion criteria, which inevitably produced selection bias. Second, our study only included a single team with an internal validation cohort. The reproducibility should be addressed in future multi-centre studies. Third, due to the irregular shape of some tumors, the ROI delineation process is difficult and time-consuming. In future studies, it will be very necessary to develop an automated or semi-automated tool to achieve effective and automatic tumor segmentation. Finally, in this study, we used different imaging instruments and acquisition parameters to complete the CT scanning. The influence of different instruments and different parameters on radiomics features is obvious. Therefore, it is important to standardise scanning protocols in different instruments and different institutions.

Conclusion

In conclusion, Triphasic enhanced CT radiomics models was constructed to predict *KRAS* mutation status in colorectal cancer, and the results showed that the AP, VP and DP models could better predict *KRAS* mutation status in the training cohort and validation cohort. The DP models showed a higher predictive performance compared to AP or VP models. Additionally, the clinical-radiomics model that incorporates both clinical risk factors and radiomics features of DP images showed good performance in predicting *KRAS* mutations. The clinical-radiomics fusion model can be used as a potential imaging marker for preoperative detection of *KRAS* mutation status, and guide the selection of molecular targeted drug therapy for CRC.

Methods

Patients

Ethical approval

had obtained by the medical ethics committee of Lanzhou University Second Hospital for this retrospective study, and the informed consent requirement was waived. All methods were carried out in accordance with relevant guidelines and regulations. For the primary cohort of this study, we analysed the institutional database in our hospital between March 2014 and June 2020 to identify eligible patients with confirmed cases of CRC who underwent curative resection. A total of 447 patients met the inclusion criteria in our study. The inclusion criteria were set based on the following factors: (1) pathologically identified cases of primary CRC adenocarcinoma; (2) patients who underwent *KRAS* mutation status testing prior to the treatment; (3) pre-treatment abdominal triphasic enhanced CT with a reconstruction slice thickness of 1.25 mm. The exclusion criteria were set based on the following factors: (1) abdominal triphasic enhanced CT was not performed before surgery or the interval between abdominal triphasic enhanced CT and surgery was > two weeks; (2) CRC patients who have received any anticancer treatment prior to the collection of pathological tissue samples; (3) insufficient CT quality for qualitative and quantitative analyses; (4) clinical information incomplete; (5) occurrence of intussusception in the area where the tumor was located. Figure 1 shows the flow diagram of the recruitment pathway. Patients were categorised into training cohort and validation cohort in 7:3 ratio.

Clinical-pathologic characteristics and semantic features

Baseline clinicopathological characteristics included age, sex, tumor location, *KRAS* mutation status, CEA level (threshold value ≥ 5 ng/mL, < 5 ng/mL), CA125 level (threshold value ≥ 35 U/ml, < 35 U/ml), and CA199 level (threshold value ≥ 37 U/ml, < 37 U/ml). These data were collected from medical records, blindly and independently by two radiologists to ensure the accuracy of the extracted data. Two experienced gastrointestinal radiologists (Y T C and J Z), analysed the images (including tumor location, maximum diameter, cT stage, and cN stage). Both radiologists were blinded to the patient's clinicopathological data. The maximum tumor thickness was defined as the maximum diameter perpendicular to the long axis of the cross-sectional image. Clinical tumor stage (cT stage) and clinical node stage (cN stage) were identified according to the 8th edition of the American Joint Committee on Cancer Staging system³⁶.

KRAS mutation evaluation

Formalin-fixed tumor tissue samples were obtained following CRC operations and confirmed that the specimens used to extract DNA are clearly infiltrated by the tumor. DNA was extracted from formalin-fixed tumor sections. *KRAS* mutation status (exons 2, 3, and 4) was detected via polymerase chain reaction (PCR).

CT Image Acquisition and segmentation

Abdominal triphasic enhanced CT scans were performed on a Discovery CT 750 HD scanner (GE Healthcare, Waukesha, WI) and iCT 256 scanner (Philips, Amsterdam, Netherlands). The scanning parameters are listed in supplementary Table S1. Enhanced CT scanning was performed using a high-pressure dual-cylinder syringe to inject intravenous iohexol (1 mL/kg) through the median cubital vein with an injection rate of 3.5-4.5 ml/second. Following the injection of contrast medium, arterial phase (AP), venous phase (VP), and delayed phase (DP) were scanned at 25-30 s, 60-70 s, and 120-150 s, respectively.

The original images of AP, VP and DP were stored in the corresponding folders in DICOM format. Two gastrointestinal radiologists (reader 1 Y T C and reader 2 J Z) performed three-dimensional (3D) radiomics segmentation on AP, VP, and DP using ITK-SNAP software (version 3.6.0; www.itksnap.org). Reader 1 segmented 247 cases, reader 2 segmented the other 200 cases.

For 3D radiomics segmentation, the ROI was manually delineated on each slice of the tumor. Air and faeces in the intestinal tract, and pericolic fat were carefully excluded from the contours (Figure 2). Finally, each patient generated three ROIs (AP ROI, VP ROI and DP ROI). To evaluate inter-observer

reproduceability and robustness of feature extraction, reader 1 and reader 2 randomly select 30 patients and do the manual segment. We estimated the reproducibility of feature extraction using inter-class correlation coefficients (ICCs) and ICCs value greater than 0.80 indicates good reproducibility³⁷. Additionally, 30 patients were randomly selected from each CT scanner to build the CT scanners set for calculating the intra-/interclass correlation coefficients (ICCs).

Feature extraction

Radiomic features were extracted and selected using PyRadiomics software³⁸. Seven classes of radiomics features (first-order histogram, 3D morphologic, grey level co-existence matrix (GLCM), grey level range-matrix (GLRM), grey level size zone matrix (GLSZM), neighbouring grey tone difference matrix (NGTDM), and grey level dependence matrix (GLDM) features) were extracted from original and filtered images (wavelet and Laplacian of Gaussian). Finally, 1037 3D radiomics features were extracted from each phase of triphasic enhanced CT. The specific definitions and descriptions of the features are demonstrated in the supplementary materials.

Feature selection and radiomics prediction model building

After radiomics features extraction, all missing data in the training cohort were replaced by median value and z-score normalisation was performed on each feature, and the same preprocessing procedure was applied to the validation cohort. After features preprocessing, the most importance features were selected to predict *KRAS* mutation using a three-step procedure. Firstly, univariate analysis was performed for feature selection to retain the feature with $p < 0.05$ to enter the following process. Secondly, the Boruta method³⁹ was used to retain the features that closely associated with *KRAS* mutations. Finally, multivariable stepwise regression further eliminates irrelevant features and retains the most informative features. A ten times five-fold cross-validation was applied to avoid overfitting and to identify the model with the best performance.

Three radiomics models (AP model, VP model, and DP model) were established based on the above radiomics signatures in triphasic phases enhanced CT images. For example, VP model was built based on VP features in 3D segmentation patterns (three features). Further, the 3D-combined model was built based on AP, VP, and DP fusion features in 3D segmentation patterns (eleven features).

Clinical and combined model construction

For clinical and imaging characteristics, the Chi-squared test or Fisher's exact test were used to compare the differences in sex, tumor location, CEA, CA125 and CA199, cT stage, and cN stage, while the Student's t-test or Mann-Whitney U test were used to compare the differences in age and maximum diameter between mutated *KRAS* and wild-type *KRAS* groups in the training cohorts. Generally, P values < 0.05 (two-sided) were considered statistically significant. We performed multivariable analyses to identify the most important features. A clinical model was established based on the inclusion of selected features.

A clinical-radiomics fusion model was developed based on correlated clinical risk factors, strong correlated imaging characteristics, and radiomics features to verify whether the combination of radiomics signatures and clinical factors could improve performance in the prediction of *KRAS* mutations. Two steps were used to build the fusion model in this study. First, AP, VP and DP models were compared to determine the enhancement phase with the best *KRAS* mutation prediction performance. Secondly, Random Forest (RF) algorithm was used to combine clinical factors, imaging characteristics, and the radiomics features of the best predictive performance phase to construct a clinical-radiomics fusion model in the training cohort, and the discriminant ability of the fusion model was evaluated by AUC value in the validation cohort.

Statistical analysis

All statistical analyses were conducted using the R statistical software package (version 3.6.3; <http://www.Rproject.org>). The Student's t-test, Mann-Whitney U test, and chi-squared test or Fisher's exact test was used to compare continuous and categorical variables, as appropriate. A two-sided P value < 0.05 was considered statistically significant. The intra-/interclass correlation coefficients (ICCs) were used to calculate the consistency of measurements between the two radiologists and different CT scanners. ROC analysis was used to evaluate the predictive accuracy of the different models. The AUC value and 95% confidence interval (CI), accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated.

Declarations

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Final approval of the manuscript: All authors

Data Accessibility

Data are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no conflicts of interest.

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Figures

Figure 1

Flow diagram of the recruitment pathway.

Figure 2

A 58-year-old female with rectal cancer was pathologically confirmed to have *KRAS* mutation. The example of tumor delineation and segmentation are shown on the arterial (a-c), venous (d-f), and delayed phase (g-i). Fig a, d and g represents the delineation of rectal cancer in the arterial, venous, and delayed phase, respectively. Fig b, e and h represents the corresponding manual region of interest (ROI) in the arterial, venous, and delayed phase, respectively. Fig c, f and i represents the whole volume extracted from the same rectal tumor.

Figure 3

ROC curves of the different models in training (A) and validation cohorts (B). AUC, area under the curve; A, radiomics model of arterial phase; D, radiomics model of delayed phase; V, radiomics model of venous phase; Radiomics, radiomics model of fusion of arterial phase, delayed phase and venous phase features; COMB, fusion of clinical risk factors and radiomics features of delayed phase.

Figure 4

Calibration curves of the different models in training (A) and validation cohorts (B). A, radiomics model of arterial phase; D, radiomics model of delayed phase; V, radiomics model of venous phase; Radiomics, radiomics model of fusion of arterial phase, delayed phase and venous phase features; COMB, fusion of clinical risk factors and radiomics features of delayed phase.

Figure 5

Decision curve analysis of different models in training (A) and validation cohorts (B). A, radiomics model of arterial phase; D, radiomics model of delayed phase; V, radiomics model of venous phase; Radiomics, radiomics model of fusion of arterial phase, delayed phase and venous phase features; COMB, fusion of clinical risk factors and radiomics features of delayed phase.

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