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Pretreatment CT and PET radiomics predicting rectal cancer patients in response to neoadjuvant chemoradiotherapy

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ABSTRACT

Background: The purpose of this study was to characterize pre-treatment non-contrast computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography (PET) based radiomics signatures predictive of pathological response and clinical outcomes in rectal cancer patients treated with neoadjuvant chemoradiotherapy (NACRT).

Materials and methods: An exploratory analysis was performed using pre-treatment non-contrast CT and PET imaging dataset. The association of tumor regression grade (TRG) and neoadjuvant rectal (NAR) score with pre-treatment CT and PET features was assessed using machine learning algorithms. Three separate predictive models were built for composite features from CT + PET.

Results: The patterns of pathological response were TRG 0 (n = 13; 19.7%), 1 (n = 34; 51.5%), 2 (n = 16; 24.2%), and 3 (n = 3; 4.5%). There were 20 (30.3%) patients with low, 22 (33.3%) with intermediate and 24 (36.4%) with high NAR scores. Three separate predictive models were built for composite features from CT + PET and analyzed separately for clinical endpoints. Composite features with $\alpha = 0.2$ resulted in the best predictive power using logistic regression. For pathological response prediction, the signature resulted in 88.1% accuracy in predicting TRG 0 *vs.* TRG 1–3; 91% accuracy in predicting TRG 0–1 *vs.* TRG 2–3. For the surrogate of DFS and OS, it resulted in 67.7% accuracy in predicting low *vs.* intermediate *vs.* high NAR scores.

Conclusion: The pre-treatment composite radiomics signatures were highly predictive of pathological response in rectal cancer treated with NACRT. A larger cohort is warranted for further validation.

Key words: rectal cancer; CT; PET; radiomics; neoadjuvant chemoradiation therapy; pathologic response

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Introduction

Neoadjuvant chemoradiation therapy (NACRT) in locally advanced rectal cancer (LARC) could improve locoregional control and downgrade tumors to facilitate surgical resection. Organ preservation ("watchful waiting") is increasingly considered as an alternative option in patients who achieve excellent response to NACRT [1]. Accurately predicting response after NACRT remains a challenge in selecting patients feasible for organ preservation management. There is an unmet need to develop non-inva-

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sive imaging biomarkers for prediction of treatment response, which could then be used for optimized patient selection and therapy personalization

Radiomics is a method for high throughput analysis of radiological images for automated extraction of clinically relevant information. Radiomics features include entire volumes texture, regional texture, focal voxel texture, and interactive properties of multiple voxels with spatial relationship such as skewness and kurtosis. It has been explored in multiple disease sites as an approach of "virtual 3D biopsy" to provide important complementary information in assessing treatment responses in various cancers and guiding clinical decisions [2–6]. T2-weighted MRI based texture analysis in rectal cancer has shown the potential to be imaging biomarkers predicting treatment response to NACRT [7, 8]. PET-derived radiomics features also have been found to be able to assess histopathologic response and predict survival in rectal cancer [9, 10]

In this study, we aimed to assess if the combined radiomics features from staging PET and pre-treatment simulation CT obtained for radiation therapy planning could predict the pattern of response and clinical outcomes in rectal cancer patients.

Materials and methods

Study design

This study was approved by the institutional review board of Moffitt Cancer Center and the University of South Florida. We screened patients with locally advanced rectal cancer who underwent pretreatment staging PET between January 1st 2011 and February 20th 2018. Sixty-six patients treated with NACRT were identified and assessed for the tumor regression grade (TRG) (0 = pCR; 1 = moderate response; 2 = partial response; 3 = poor response) by a gastrointestinal pathologist according to College of American Pathologists criteria. Complete responders (TRG 0) *vs.* non-complete responders (TRG 1-3) and favorable responders (TRG 0-1) *vs.* unfavorable responders (TRG 2-3) were assessed with the radiomics algorithm. The clinical outcome surrogate — neoadjuvant rectal (NAR) score was assessed using the previously published and clinically validated algorithm [11]. The NAR cutoff points for low, intermediate, and high NAR scores (NAR < 8 *vs.* NAR = 8–16 *vs.* NAR > 16) were adopted from the previously validated values using the NSABP R-04 trial dataset [11]. Clinical parameters including age, gender, staging, and treatment approaches were reviewed.

Pre-treatment simulation CT from radiation treatment planning and staging PET of patients were retrospectively reviewed. The volume of Interest (VOI) incorporated the primary tumor as delineated on CT and PET by a radiation oncologist who specialized in gastrointestinal cancer (Fig. 1A). Air in the delineated VOI was subtracted manually for feature extraction.

Radiomics features

Radiomics features were extracted from the segmented primary disease individually from PET and readily available RT planning non-contrast CT images using an in-house algorithm, including intensity, shape, gray-level co-occurrence matrix (GLCM), gray-level run-length matrix (GLRLM), gray-level size-zone matrix (GLSZM), neighborhood gray-tone difference matrix (NGTDM), LoG, wavelet, Laws and Fractal dimension (FD). A composite feature as described in our previous study [13], α*PETf + (1-α)*CTf, $0 \leq \alpha \leq 1$, was constructed for each corresponding CT and PET dataset. In this study, three α values (0.2, 0.5, and 0.8) were applied for analysis with α of 0.2 generating the best performance. For each case, a total of 929 radiomic features were extracted from CT and PET images. The same number of composite features was further obtained for each case with individual α value.

Statistics

Machine learning models were built using Weka-based algorithms (Weka, version 3.6.15, Hamilton, New Zealand). Radiomic features predictive of TRG or NAR were selected by the logistic regression model with a dependent response variable. The subset selection with correlation-based feature was performed according to the value of a subset of attributes by considering the individual predictive ability of each feature along with the degree of redundancy between them. Highly correlated features were removed based on the order of area under the curve (AUC) of receiver operating characteristics curve (ROC) versus the TRG groupings [16]. Features with the Pearson correlation coefficient being less than 0.65 were used to build each predictive model. The features were then selected as input variables to build predictive models using ma-

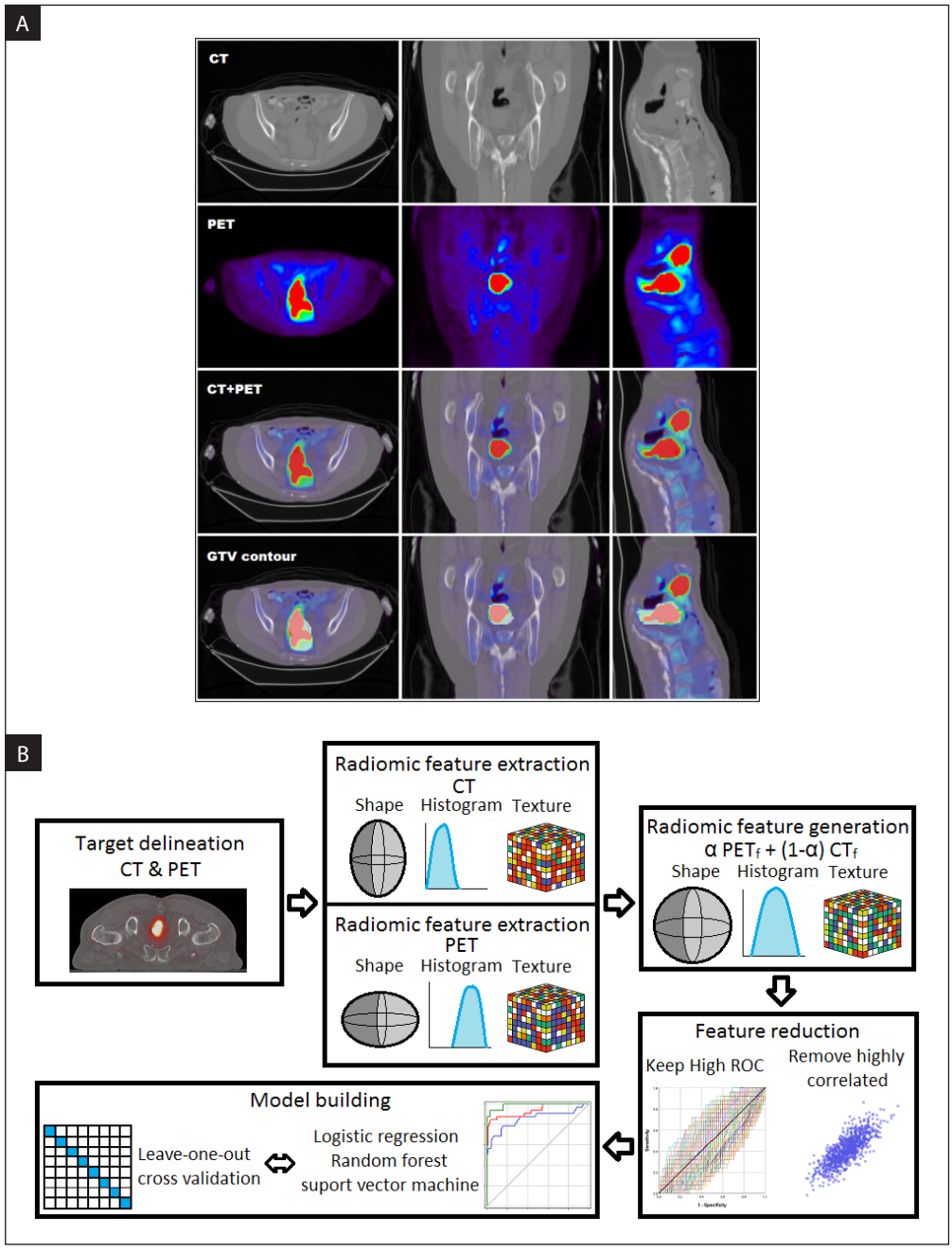

Figure 1. The radiomic process in patient with rectal cancere, treated with NACRT. CT and 18-F FDG-PET images were used for tumor delineation (segmentation) creating a volume of interest (VOI). Shape-based and quantitative features are then extracted from the VOI, which were combined to generate the predictive model for clinical outcome. **A.** Gross tumor volumes (GTV) were contoured with CT and PET imaging in rectal cancer cases. **B.** Radiomic features from CT and PET imaging were extracted. Prediction models were built using logistic regression, random forest (RF) and support vector machine (SVM) methods, and leave-one-out validation (LOOV) was performed

chine learning algorithms with logistic regression, random forest (RF) and support vector machine (SVM) methods. Validation was performed utilizing the leave-one-out cross validation (LOOCV) approach. LOOCV is a well-established approach to validate a model for small size of cohort, which allows to build models based on N-1 cases and the model is validated with the one left out in the model building process. With LOOCV approach, the final model is built and validated for N times. The feature reduction and model building/validation was performed for every different α value (Fig. 1B).

A confusion matrix was determined to utilize the assignments from response patterns in correlation with TRG and NAR. The accuracy, sensitivity and specificity were derived from the confusion matrix for the leave-one-out cross-validation.

Results

Sixty-six patients with rectal cancer treated with NACRT were reviewed retrospectively. The patient and tumor characteristics are summarized in Table 1. Median follow-up from the end of NACRT was 27.9 months. The median age of patients was 56 (range: 29-80) and the majority were white (n = 61; 92.4%). Patients most commonly presented with clinical T3 (cT3, n = 57; 86.4%) and node-positive disease (n = 42; 63.7%). Patients received concurrent Fluorouracil or Capecitabine-based CRT. RT was delivered to a median prescribed dose of 45 Gy to the pelvis and 50.4 Gy to the primary disease.

Table 1. Patient, tumor and treatment characteristics of rectal cancer patients

Variables	Number	%
No. of patients	66	
Follow-up (months)		
Median	25.5	
Range	2.5–90.5	
Age		
Median	56	
Range	29–80	
Gender		
Male	38	57.6
Female	28	42.4
Race		
White	61	92.4
Other	5	7.6
Clinical T stage		
cT1	1	1.5
cT2	3	4.5
cT3	57	86.4
cT4	5	7.6
Clinical nodal stage		
cN0	24	36.4
cN1	37	56.1
cN2	5	7.6
Distant metastasis		
cM0	66	100.0
cM1	0	0.0
Pathological T stage		
ypT0	13	19.7
ypT1	5	7.6
ypT2	13	19.7
ypT3	31	47.0
ypT4	2	3.0
ypTis	2	3.0
Pathological nodal stage		
ypN0	40	60.6
ypN1	21	31.8
ypN2	5	7.6
Concurrent chemotherapy		
5-FU	47	71.2
Capecitabine	19	28.8
Pelvic RT dose (Gy)	45.0	
RT dose to primary disease (Gy)		
Median	50.4	
Range	45–56	
Interval from end of CRT to surgery		
Median	59	
Range	36–103	

5-FU — 5-fluorouracil; RT — radiotherapy; CRT — chemoradiotherapy

In this cohort, thirteen patients (19.7%) achieved a pathologic complete response (pCR, TRG 0), thirty-four with TRG 1 (51.5%), sixteen with TRG 2 (24.2%), and three with TRG 3 (4.5%). There were twenty patients (30.3%) with low, twenty-two (33.3%) with intermediate and twenty-four (36.4%) with high NAR scores. Lower NAR score would represent a better overall survival as previously described [11]. According to historic data, TNM staging was prognostic for clinical outcome. However, it could not predict pathological response. This study utilized the advantage of radiomics analysis to predict pathological response by dissecting the detailed radiomics features.

Three separate predictive models were built for composite features from CT+PET and analyzed separately for clinical endpoints (TRG and NAR). Composite features with $\alpha = 0.2$ resulted in the best predictive power using logistic regression compared with RF and SVM. We found that a 4-feature model

Table 2. Computed tomography (CT) and positron-emission tomography (PET)-based radiomics predicting outcomes

Machine learning algorithm	No. of radiomics features	Predicting parameters	Accuracy	ROC	σ_{max}
Composite features with α = 0.2 using logistic regression	4	TRG 0 *vs.* TRG 1–3	88.1%	0.858	0.097
	6	TRG 0–1 *vs.* TRG 2–3	91.0%	0.951	0.050
	11	Low *vs.* Intermediate *vs.* High	67.7%	0.814	0.123

TRG — tumor regression grade; ROC — receiver operating characteristics curve

resulted in 88.1% accuracy (sensitivity of 77.8%, specificity of 89.7%, ROC 0.858) in predicting TRG 0 *vs.* TRG 1-3 (Tab. 2). The four features included LoG.5norm entropy, LoG2.5min, lLLSenergy, and CoCCluster Shade. A 6-feature model resulted in 91% accuracy (sensitivity of 93.8%, specificity of 84.2%, ROC 0.951) in predicting TRG 0-1 *vs.* TRG 2-3 (Tab. 2). The six features were LoG.5Skewness, LoG2CoeffVari, RL-HGRE, RL-LRHGE, SZ-LAE, and SZ-LIE. An 11-feature model resulted in 67.7% accuracy in predicting low *vs.* intermediate *vs.* high NAR scores with ROC 0.814 (Tab. 2). The eleven features were lLSSuniformity, CoCClusger Shade, wLHHhist entropy, wLHLentropy, RL-LRHGE, lELLnorm contrast, GTD-Coarseness, lSELpeak, wLLHnorm entropy, wHLHnorm entropy, and LoG.5Skewness. The other clinical features, such as tumor volume and length, were not predictive in the radiomic features analysis.

Discussion

In this study, we demonstrated that the combination of radiomics features derived from the pretreatment CT and PET images were highly predictive of response patterns in rectal cancer treated with NACRT. These non-invasive and easily accessible imaging biomarkers could provide a promising way to predict complete responders and select patients for nonoperative management.

Radiomics utilizes massive imaging data with machine learning algorithm to exploit potential clinical application to optimize patient selection and outcomes. Imaging texture analysis has been well studied in clinical oncology by analyzing the grey-level patterns and voxel intensity-spatial relationship [14, 15]. Multiple studies have explored the capability of PET-based textural parameters of rectal cancer heterogeneity as a predictive and prognostic factor in evaluating treatment response [10, 12]. Bundschuh et al. reported that pre- and post-treatment PET-based coefficient of variation could predict early and late response in rectal cancer treated with NACRT [10]. Giannini et al. demonstrated that the combination of PET and MRI radiomics features (5 from PET and 1 from T2W MRI) could distinguish between responders and nonresponders with an AUC of 0.86, sensitivity of 86% and specificity of 83% in a cohort of rectal cancer patients treated with NACRT (n = 52).

Our study in a cohort of 91 rectal cancer patients showed that eight radiomics features from pre-treatment non-contrast CT could differentiate responders and non-responders with an accuracy of 84% [13]. In the current study, we found that the combination of pretreatment CT and PET radiomics features could slightly improve the predictive accuracy to 88.1% in differentiating responders and non-responders with only four features. This radiomics-based pretreatment risk stratification would potentially enable physicians to pursue more tailored patient-specific treatment approach. These radiomics features could serve as a noninvasive biomarker for patient stratification and selection for nonoperative management. A larger study is needed to improve the power and reliability with the goal to personalize therapeutic approach and avoid unnecessary treatment.

There are some limitations to this study. First, this is a single institute retrospective study. The radiomics features should be validated on a larger imaging dataset in a multicenter setting prospectively. Second, the machine learning algorithm should be assessed on images from different scanners. Third, despite the fact that rectal MRI has been widely adopted to evaluate rectal cancers, the majority of the patients from this cohort did not have a pretreatment MRI for radiomics analysis. Future studies incorporating MRI, CT, and PET texture parameters could potentially lead to an optimal discriminant performance in predicting treatment response in rectal cancer treated with NACRT. In addition, we

found that eleven radiomics features resulted in 67.7% accuracy in predicting overall survival according to the NAR score stratification. A larger dataset is needed to improve the power in the prediction of clinical outcome. Currently, a multi-institute collaborative project is in the development to further validate the algorithm. As a proof of concept study, the methodology developed from this study will facilitate our future studies utilizing various radiomics features including MRI parameters. Currently, a cohort of patients with LARC are undergoing treatment with Viewray MRI-LINAC based adaptive planning at our institute. We are prospectively collecting the adaptive MRI parameters for future radiomics analysis.

Conclusion

The composite radiomics features from pretreatment non-contrast CT obtained for radiation planning and staging PET have a high accuracy in predicting responders and non-responders in rectal cancer treated with NACRT. It is promising that these easily accessible noninvasive imaging biomarkers could be introduced into daily practice for patient selection in a nonoperative approach.

Conflicts of interest

None were declared.

Funding

None were declared.

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