Radiology Science

Review

Radiomics prediction of response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer

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Abstract

Rectal cancer (RC) is one of the most common cancers worldwide. RC has high morbidity and mortality rates, with locally advanced rectal cancer (LARC) accounting for > 30% of cases. Patients with LARC are routinely treated with neoadjuvant chemoradiotherapy (nCRT) but treatment outcomes vary greatly. It is crucial to predict and evaluate patient response to nCRT as early as possible. Radiomics is a potentially useful and non-invasive tool for clinical applications in different types of cancer including colorectal cancer. Radiomics has recently been used to predict treatment outcomes and many published studies have demonstrated the efficacy of radiomics. This review will discuss the application of radiomics in predicting of LARC response to nCRT and provide new insight for corollary studies.

Keywords: AI Image Processing, MRI Technology, CT Technology

1. INTRODUCTION

Colorectal cancer is the third most common cancer worldwide and has a high mortality rate [1, 2]. Approximately 30% of all colorectal cancers are rectal cancers (RCs) [3]. Clinical stage T3/4 or N+ RC is referred to as locally advanced rectal cancer (LARC) [4]. LARC has a high rate of distant recurrence and a low survival rate despite the availability of different treatment options. Local recurrence or RC, however, is considerably less frequent than distant recurrence [5, 6]. One of the recommended treatments for LARC patients is neoadjuvant chemoradiotherapy (nCRT), followed by total mesorectal excision (TME) [6-8]. However, there are significant variations in the treatment response, ranging from no response (NR) to pathologic complete response (PCR) [9], which may be attributed to patient individuality and tumor heterogeneity. PCR is reported to occur in 15%–27% of patients after nCRT [10]. Such patients may benefit from a wait-and-see strategy as opposed to surgery to avoid surgical complications [11, 12]. Recent studies have also reported no discernible difference between patients with PCR who undergo a watch-and-wait approach versus surgery with respect to overall survival or non-regrowth cancer recurrence [13, 14]. Additionally, some patients who do not achieve PCR are still able to reduce tumor size and improve after treatment [15, 16], indicating a good response (GR) with better tumor resectability. For patients who have a NR after nCRT it is essential to modify treatment plans to avoid side effects brought on by ineffective treatment [17, 18].

The pathologic tumor regression grade (TRG) is currently utilized for assessing the therapeutic response to nCRT. There are several grading systems, including the Mandard [19], Dworak [20], and AJCC systems [21], which are accepted norms. These systems evaluate regression grades using specimens from neoadjuvant rectal cancer resections. The pathologic assessment is thought to be accurate and reliable but cannot be used for the early identification of patients who may benefit from nCRT because the specimen can only be resected and assessed after nCRT and surgery [22].

Radiomics is a high-throughput technology that extracts and utilizes quantitative features from medical images to improve the accuracy of diagnosis and prognosis in clinical decision-making systems [23-25]. In recent years an increasing number of studies have used radiomics to build models that have produced

encouraging results that predict the LARC response after nCRT [26-28]. These models can help with the early identification of patients with different therapeutic responses (PCR, GR, and NR) and aid in the development of individualized care.

This article will introduce the radiomics applications, challenges, and potential, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT), for preoperative tumor response prediction in patients with LARC after nCRT.

2. RADIOMICS

Radiomics can be divided into traditional and deep learning-based radiomics; the former uses different machine learning techniques, while the latter uses deep learning techniques. The automatic learning data representation is the primary difference between traditional and deep learning-based radiomics [29].

2.1 Traditional radiomics

The workflow of traditional radiomics (**Figure 1**) can be summarized as follows [23, 30]: (a) Image collection is the collection of complete and high-quality imaging data, which are the foundation of a successful radiomics. (b) Image segmentation in the region of interest (ROI) is obtained by outlining the tumors. There are three ways to obtain the ROI (manually, semi-automatically, and automatically). The tumor can be delineated along continuous slices or on the image layer with the largest possible tumor size. (c) Radiomics feature extraction and selection within the entire ROI is used to extract hundreds of radiomics features. The radiomics features can be divided into five categories (first-order features, texture features, shape features, transform-based features, and model-based features). Then, features are further selected to prevent overfitting as a process of feature dimension reduction using different machine learning techniques, such as least absolute shrinkage and selection operator (LASSO), principal component analysis (PCA), and max-relevance and min-redundancy (mRMR). (d) Model construction is performed when selected radiomic features are used to develop models that predict clinical events, such as the clinical stage of a tumor, how well the tumor responds to treatment, and the prognosis. Clinical parameters may also be included in the models to improve predictive performance. Popular machine learning models, including logistic regression (LR), random forest (RF), and support vector machine (SVM), along with other different techniques have a significant impact on the final prediction performance. Therefore, nearly all studies use multiple methods to evaluate the performance of developed models, such as receiver operating characteristic (ROC) curve, sensitivity, specificity, calibration curve, and decision curve analysis (DCA). (e) Model application occurs when the developed radiomics models are used to assist clinicians in realizing the individualized treatment of patients.

2.2 Deep learning-based radiomics

Deep learning represents a class of deep neural network structures based on numerous algorithm layers that can automatically learn useful features and representations from raw data, then perform accurate data analysis [31]. In recent years radiomics models based on deep learning have developed rapidly and have been widely used [32, 33].

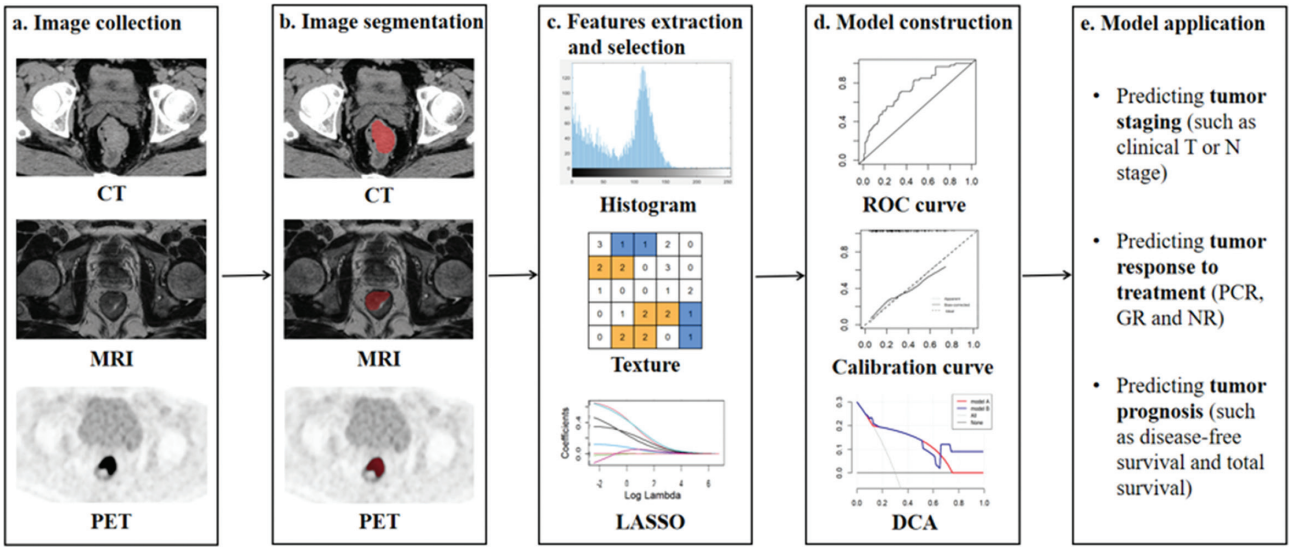

Figure 1 | Traditional radiomics workflow.

Deep learning can be roughly categorized into supervised, unsupervised, and semi-supervised learning depending on whether training dataset labels are present [34]. Supervised learning algorithms include convolutional neural networks (CNNs) and recurrent neural networks (RNNs). CNNs are widely used deep learning networks in medical image analysis. The typical architecture of CNNs include convolutional, pooling, and fully connected layers. A typical CNN directly takes an image as input, extracts features from the convolution and pooling layers, and finally maps the extracted features into output via fully connected layers [35]. Unsupervised learning methods mainly include autoencoders, generative adversarial networks, and restricted Boltzmann machines. This technique makes it possible to implement the deep learning process in the absence of labels. The common semi-supervised learning (SSL) method includes consistency regularization-, pseudo-labeling-, and generative model-based approaches. The SSL method combines labeled and unlabeled data and is applied to scenarios where labeled data are scarce. If sufficient unlabeled data are provided, the additional information unlabeled data carries about prediction could help improve model performance.

Compared with traditional radiomics, deep learning methods can extract and select supplementary high-dimensional features through automatic learning neural networks, which obtain robustness of the usual input data variations [36, 37]. This characteristic enables deep learning models to mine image information more comprehensively.

3. RADIOMICS IN PREDICTION OF LARC PATIENT RESPONSE AFTER NCRT

All relevant studies that used radiomics to predict the response of patients with LARC to nCRT and were published in the Web of Science database (https://www.webofscience.com) before August 2022 were searched and reviewed. Review articles and conference abstracts were excluded. The keywords used for the search included rectal cancer, radiomics, neoadjuvant chemoradiotherapy, response, nCRT, and LARC. Sixty studies were identified for analysis, including 46 MRI, 7 CT, 2 PET/CT, and 5 multimodal radiomics studies. Various models that predict PCR, GR, and NR will be assessed below.

3.1 Radiomics in PCR prediction

PCR is defined as few or no remaining invasive cancer cells in the rectal cancer resection specimen and indicates the absence of residual tumor after nCRT treatment [9, 20, 38]. Patients who achieve a PCR have a higher likelihood of preserving their sphincters, which would completely alter their treatment regimen and improve the quality of life [39-41]. It is important from a clinical perspective to identify significant factors that predict PCR following preoperative nCRT. **Table 1** provides an overview of the major studies that recommend radiomics for PCR prediction after nCRT.

Several studies are currently investigating radiomics models in PCR prediction, the majority of which focus on MRI images. MRI is the preferred modality for staging and evaluating rectal cancer because MRI provides excellent spatial resolution and superb soft tissue contrast with respect to structural detail of the rectum and surrounding structures, such as the lumen, mesorectum, and nodes [76-79]. Previous studies commonly extracted radiomics features from T2WI images to develop prediction models. Rectal lesions are well-localized by T2WI, which facilitates accurate ROI delineation and reduces variability caused by manual delineation by different radiologists. Li et al. [46] used pre- and pro-treated T2WI LARC images to develop the models. Li et al. [46] extracted first-order, shape, texture, and transform-based features from these images and the model demonstrated its predictive ability with an AUC of 0.945 and a sensitivity of 0.857 in the training set with cross-validation. The small sample size and absence of external validation datasets question whether the robust generalization of the model can be guaranteed.

Additional sequences, including DWI, ADC, and CE-TIWI, aid in tumor biological process quantification, such as microcirculation, vascular permeability, and tissue cellularity [76]. Using multiple sequences might improve the performance of radiomics models even though the findings of existing studies are not in agreement. One meta-analysis [80] concluded that MRI assessment, which combines T2WI and DWI, performs better than T2WI alone in predicting PCR after nCRT in LARC patients. However, Shin et al. [56] demonstrated that the T2-weighted model outperforms the radiomics model based on T2WI and ADC ($AUC_{T2WI+ADC}$ = 0.82, AUC_{T2WI} = 0.82; $P > 0.05$) with respect to classification performance of PCR and non-PCR but did not show the advantages of models using multiple sequences.

Additionally, developing a model that incorporates radiomics features and clinical parameters may improve model performance for prediction and classification but also produces results that are currently inconsistent across studies [42, 50]. It is essential to explore the predictive effectiveness of clinical variables and multiparametric radiomics in large-scale and multicenter studies. However, existing studies typically lack extensive external validation and prospective studies, which are common limitations. A prospective study by Feng et al. [61] using three different sequences (T2WI, DWI, and CE-T1WI) and 1033 patients yielded promising predictive results in two external validation sets, which ensured the generalizability and reliability of the established models.

A CT scan is frequently the preferred examination for initial staging of rectal cancer [76]. Despite having less soft tissue contrast than MRI, CT has its own advantages in conducting radiomics studies due to robust volumetric data, which has high reproducibility across different

Table 1 | Summary of radiomics applications for predicting PCR after nCRT.

Study	Year	Imaging modality	Image timing	Design	No. of patients	Feature type	Developed model	AUC*
Song et al. [42]	2022	T2WI	Pre-nCRT	Retrospective Multi-center	674	Radiomics and clinical features	DT SVM	0.9891
Boldrini et al. [43]	2022	T2WI	Pre-nCRT	Retrospective Multi-center	221	Radiomics and clinical features	LR	0.73
Tang et al. [44]	2022	T2WI	Pre-nCRT	Retrospective Multi-center	88	Radiomics and clinical features	GLM	0.831
Chiloiro et al. [45]	2021	T2WI	Pro-nCRT	Retrospective Single center	144	Radiomics features	LR	0.84
Li et al. [46]	2021	T2WI	Pre-nCRT Pro-nCRT	Retrospective Single center	80	Radiomics features	LR RF DT KNN	0.945
Delli et al. [47]	2021	T2WI	Pre-nCRT	Retrospective Single center	72	Radiomics and clinical features	PLS regression	0.793
Pang et al. [48]	2021	T2WI	Pro-nCRT	Retrospective Multi-center	275	Radiomics features	SVM	0.924
Cusumano et al. [49]	2021	T2WI	Pre-nCRT	Retrospective Multi-center	195	Radiomics features	RF	0.72
Petkovska et al. [50]	2020	T2WI	Pre-nCRT	Retrospective Single center	102	Radiomics and clinical features	SVM	0.75
Shaish et al. [51]	2020	T2WI	Pre-nCRT	Retrospective Multi-center	132	Radiomics and clinical features	LR	0.8
Antunes et al. [52]	2020	T2WI	Pre-nCRT	Retrospective Multi-center	104	Radiomics features	RF	0.699
Li et al. [53]	2019	T2WI	Delta-nCRT	Retrospective Single center	131	Radiomics features	LR	0.92
Yi et al. [54]	2019	T2WI	Pre-nCRT	Retrospective Single center	134	Radiomics and clinical features	SVM	0.9078
Ferrari et al. [55]	2019	T2WI	Pre-nCRT Mid-nCRT Pro-nCRT	Retrospective Single center	55	Radiomics features	RF	0.86
Dinapoli et al. [39]	2018	T2WI	Pre-nCRT	Retrospective Multi-center	221	Radiomics and clinical features	LR	0.73
Shin et al. [56]	2022	T2WI ADC	Pro-nCRT	Retrospective Single center	898	Radiomics features	LR	0.89
Wan et al. [57]	2021	T2WI DWI	Delta-nCRT	Retrospective Single center	165	Radiomics features	LR	0.91
Zhang et al. [58]	2020	T2WI DKI	Pre-nCRT Pro-nCRT	Prospective Single center	383	Radiomics features	CNN	0.997
Liu et al. [59]	2017	T2WI DWI	Pre-nCRT Pro-nCRT	Retrospective Single center	222	Radiomics and clinical features	SVM	0.9799
Nardone et al. [60]	2022	T2WI DWI ADC	Delta-nCRT	Retrospective Multi-center	100	Radiomics features	LR	0.87
Feng et al. [61]	2022	T2WI DWI CE-T1WI	Pre-nCRT	Retrospective and prospective Multi-center	1033	Radiomics and clinical features	SVM	0.868

Table 1 | Continued

Study	Year	Imaging modality	Image timing	Design	No. of patients	Feature type	Developed model	AUC*
Cheng et al. [62]	2021	T1WI T2WI T2WI-FS	Pre-nCRT	Retrospective Single center	193	Radiomics and clinical features	LR	0.959
Lee et al. [63]	2021	MSFI	Pre-nCRT	Retrospective Single center	912	Radiomics features	RF	0.837
Shi et al. [64]	2020	T2WI ADC CE-T1WI	Pre-nCRT Mid-nCRT	Retrospective Single center	51	Radiomics features	ANN CNN	0.86
Van Griethuysen et al. [65]	2020	T2WI DWI ADC	Pre-nCRT	Retrospective Multi-center	133	Radiomics features	LR	0.73-0.77
Bulens et al. [66]	2019	T2WI DWI ADC	Pre-nCRT Pro-nCRT	Retrospective Multi-center	125	Radiomics features	LASSO	0.86
Cui et al. [67]	2018	T2WI ADC CE-T1WI	Pre-nCRT	Retrospective Single center	186	Radiomics and clinical features	LR	0.948
Nie et al. [68]	2016	T1WI T2WI ADC CE-T1WI	Pre-nCRT	Retrospective Single center	48	Radiomics features	ANN	0.84
Mao et al. [69]	2022	CE-CT	Pre-nCRT	Retrospective Single center	216	Radiomics and clinical features	LR	0.926
Zhuang et al. [70]	2021	CE-CT	Pre-nCRT	Retrospective Single center	177	Radiomics and clinical features	LR SVM GBM	0.997
Bibault et al. [71]	2018	CE-CT	Pre-nCRT	Retrospective Multi-center	95	Radiomics and clinical features	DNN SVM LR	0.72
Yuan et al. [72]	2020	Non-contrast CT	Pre-nCRT	Retrospective Single center	91	Radiomics features	LR RF SVM	No AUC; accuracy, 83.90%
Hamerla et al. [73]	2019	Non-contrast CT	Pre-nCRT	Retrospective Single center	169	Radiomics features	RF	No AUC; accuracy, 87%
Capelli et al. et al. [74]	2022	T2WI ADC PET/CT	Pre-nCRT	Retrospective Single center	50	Radiomics features	LR	0.863
Bordron et al. [75]	2022	CE-CT T2WI DWI	Pre-nCRT	Retrospective Multi-center	124	Radiomics and clinical features	NNC	0.95

T2WI, T2-weighted imaging; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; DKI, diffusion kurtosis imaging; CE-TIWI, contrast-enhanced T1-weighted imaging; T1WI, T1-weighted imaging; T2WI-FS, T2-weighted imaging fat suppression; MSFI, multi-sequence fusion images; CE-CT, contrast-enhanced computed tomography; PET/CT, positron emission tomography/computed tomography; nCRT, neoadjuvant chemoradiotherapy; DT, decision tree; SVM, support vector machine; LR, logistic regression; GLM, generalized linear model; RF, random forest; KNN, K-nearest neighbors; PLS regression, partial least square regression; CNN, convolutional neural network; ANN, artificial neural network; LASSO, least absolute shrinkage and selection operator; GBM, gradient boosting machine; DNN, deep neural networks; NNC, neural network classifier; *The AUC is from the top-preformed model of the training set.

Table 2 | Summary of radiomics applications for predicting GR after nCRT.

Study	Year	Imaging modality	Image timing	Design	No. of patients	Feature type	Developed model	AUC*
Filitto et al. [83]	2022	T2WI	Pre-nCRT	Retrospective Single center	39	Radiomics features	SVC	0.89
Chen et al. [84]	2022	T2WI	Pre-nCRT	Prospective Single center	137	Radiomics and clinical features	LR	0.871
Horvat et al. [85]	2022	T2WI	Pre-nCRT	Retrospective Multi-center	164	Radiomics features	RF	0.83
Jeon et al. [86]	2020	T2WI	Pre-nCRT	Retrospective Single center	135	Radiomics and clinical features	EN	0.785
Yi et al. [54]	2019	T2WI	Pre-nCRT	Retrospective Single center	134	Radiomics and clinical features	SVM	0.9017
Tang et al. [87]	2019	DWI	Pre-nCRT Pro-nCRT	Retrospective Single center	222	Radiomics and clinical features	LR	0.893
Wan et al. [88]	2022	T2WI DWI	Pre-nCRT Pro-nCRT	Retrospective Single center	153	Radiomics and clinical features	LR	0.93
Zhang et al. [89]	2021	T2WI CE-T1WI	Pre-nCRT	Retrospective Single center	189	Radiomics and clinical features	RF SVM KNN EC	0.97
Liu et al. [90]	2021	T2WI CE-T1WI	Pre-nCRT	Retrospective Multi-center	189	Radiomics and clinical features	SVM	0.9371
Chen et al. [91]	2021	ADC APTw	Pre-nCRT Pro-nCRT	Retrospective Single center	53	Radiomics features	LR	0.895
Zhang et al. [58]	2020	T2WI DKI	Pre-nCRT Pro-nCRT	Prospective Single center	383	Radiomics features	CNN	0.99
Wang et al. [92]	2022	T2WI DWI CE-T1WI	Pre-nCRT	Retrospective Single center	207	Radiomics features	DT RF SVM LR Adaboost	0.923
Wang et al. [93]	2020	T2WI ADC CE-T1WI	Pre-nCRT	Retrospective Single center	183	Radiomics and clinical features	RF LR	0.923
Cheng et al. [62]	2021	T1WI T2WI T2WI-FS	Pre-nCRT	Retrospective Single center	193	Radiomics and clinical features	LR	0.918
Shi et al. [64]	2020	T2WI ADC CE-T1WI	Pre-nCRT Mid-nCRT	Retrospective Single center	51	Radiomics features	ANN CNN	0.93
Van Griethuysen et al. [65]	2020	T2WI DWI ADC	Pre-nCRT	Retrospective Multi-center	133	Radiomics features	LR	0.69-0.79
Nie et al. [68]	2016	T1WI T2WI DWI CE-T1WI	Pre-nCRT	Retrospective Single center	48	Radiomics features	ANN	0.89

Table 2 | Continued

Study	Year	Imaging modality	Image timing	Design	No. of patients	Feature type	Developed model	AUC*
Bonomo et al. [94]	2022	Simulation CT	Pre-nCRT	Retrospective Multi-center	201	Radiomics features	RF LR SVM DT KNN GNB	0.65
Wu et al. [95]	2021	PET/CT	Pre-nCRT	Retrospective Single center	236	Radiomics features	SVM	0.96

T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; CE-TIWI, contrast-enhanced T1-weighted imaging; ADC, apparent diffusion coefficient; APTw, amide proton weighted; DKI, diffusion kurtosis imaging; T1WI, T1-weighted imaging; T2WI-FS, T2-weighted imaging fat suppression; PET/CT, positron emission tomography/computed tomography; nCRT, neoadjuvant chemoradiotherapy; SVC, support vector classifier; LR, logistic regression; RF, random forest; EN, elastic net; SVM, support vector machine; KNN, K-nearest neighbors; EC, ensemble classifier (including RF, SVM, and KNN); CNN, convolutional neural network; DT, decision tree; ANN, artificial neural network; GNB, Gaussian naïve-Bayes; *The AUC is from the top-preformed model of the training set.

patients [81]. Indeed, few studies have used CT radiomics models to predict PCR; however, the models developed using contrast-enhanced CT (CE-CT) or non-enhanced CT (NE-CT) achieved good results in these studies. The clinical-radiomics model developed by Zhuang et al. [70] included radiomics features extracted from pre-treatment CE-CT images as well as clinical parameters, such as carcinoembryonic antigen (CEA), mesorectal fasciae (MRF), and tumor thickness. The model had an AUC of 0.997 and an accuracy of 97.3%. Yuan et al. [72] developed a predictive model using a variety of machine learning techniques with NE-CT scans that were acquired before treatment. The top model was developed using an RF classifier, with an accuracy of 83.90% in the independent validation cohort, suggesting the potential predictive value of NE-CT radiomics. NE-CT images are more accessible than CE-CT and MR images, which lowers the clinical application restriction for radiomics.

Multimodal radiomics has been used in some studies to develop prediction models by extracting and selecting features from various images, such as CT, MRI, and PET. Capelli et al. [74] developed a logistic regression model that combines T2WI, ADC images, and PET-CT images. This model successfully separated patients with and without PCR (AUC = 0.863); however, in the absence of external validation, only a small dataset was used to test model repeatability and generalizability. In another study [75], a PCR prediction model was developed by combining clinical signatures and radiomics features from multimodality images (CE-CT, T2WI, and DWI) and multicenter datasets. The final model delivered satisfactory results after using ComBat and synthetic minority over-sampling technique (SMOTE) approaches to harmonize inter-institution heterogeneity and imbalanced data. It is intriguing that none of the radiomic features extracted from CE-CT were retained after features selection, which failed to demonstrate the benefits of multimodality images. The value of a CT-based radiomics model was investigated by Zhuang et al. [70]. According to Zhuang et al. [70], a multimodal radiomics model that combines a CT- and MRI-based rad-score performs superior to a model that uses only CT or MRI. There is currently a lack of multimodal imaging research and the findings from various studies are quite inconsistent, so additional research is needed to determine the potential predictive value of multimodal radiomics.

3.2 Radiomics in GR prediction

GR is the presence of cancer cells that have not completely disappeared along with fibrosis in neoadjuvant rectal cancer resection specimens [38]. For patients who achieve a GR, the likelihood of local and distant metastases is decreased [82]. Specifically, tumors are staged less severely in 50%–60% of LARC patients after receiving nCRT [5]. **Table 2** provides a summary of the major studies that support radiomics for the prediction of a GR after nCRT.

Zhang et al. [89] developed a nomogram that integrates CE-T1WI, T2WI images, and clinical signatures, such as CEA and tumor diameter. The nomogram demonstrated accurate prediction of a GR and non-GR in both training and validation cohorts with AUC values of 0.970 and 0.949, respectively. In another study conducted in a single center, Jeon et al. [86] developed a clinical-radiomics model based on T2WI images and blood biomarkers with an AUC of 0.785, which effectively distinguished between patients who did and did not achieve a GR. Additionally, according to Jeon et al. [86], both blood biomarkers and radiomics features provide useful information for prediction, with the latter having a higher relative predictive power.

3.3 Radiomics in NR prediction

An NR is the absence of regressive alterations in neoadjuvant rectal cancer resection specimens [38]. Among patients with an NR, nCRT is ineffective and patients should be more aware of the potential side effects of receiving nCRT, such as sexual, urinary, and intestinal dysfunction [96-98]. As a result, identifying potential patients with an NR before receiving nCRT can help modify the treatment plan to lessen any side effects from ineffective therapy. A summary of the major studies supporting radiomics for the prediction of an NR after nCRT is presented in Table 3.

Zhang et al. [105] developed an LR model using CE-CT features and clinical biomarkers, which demonstrated satisfactory performance in predicting an NR with an AUC of 0.924 and a sensitivity of 88.00%. In another

Table 3 | Summary of radiomics applications for predicting NR after nCRT.

Study	Year	Imaging modality	Image timing	Design	No. of patients	Feature type	Developed model	AUC*
Shayesteh et al. [99]	2021	T2WI	Pre-nCRT Pro-nCRT Delta-nCRT	Retrospective Multi-center	53	Radiomics features	KNN NB RF XGB	0.96
Coppola et al. [100]	2021	T2WI	Pre-nCRT	Retrospective Single center	40	Radiomics features	ROC curve	0.9
Petresc et al. [101]	2020	T2WI	Pre-nCRT	Retrospective Single center	67	Radiomics and clinical features	LR	0.97
Ferrari et al. [55]	2019	T2WI	Pre-nCRT Mid-nCRT Pro-nCRT	Retrospective Single center	55	Radiomics features	RF	0.83
Su et al. [102]	2022	T2WI DWI	Pre-nCRT	Retrospective Single center	62	Radiomics and clinical features	LR	0.979
Defeudis et al. [103]	2022	T2WI ADC	Pre-nCRT	Retrospective Multi-center	95	Radiomics features	SVM BM EL LR	0.9
Zhou et al. [104]	2019	T1WI T2WI ADC CE-T1WI	Pre-nCRT	Retrospective Single center	425	Radiomics and clinical features	LR	0.822
Zhang et al. [105]	2022	CE-CT	Pre-nCRT	Retrospective Single center	215	Radiomics and clinical features	EL LR	0.924
Karahan et al. [106]	2020	PET/CT	Pre-nCRT	Retrospective Single center	110	Radiomics and clinical features	LR	0.838
Shahzadi et al. [107]	2022	T2WI Non-contrast CT	Pre-nCRT	Retrospective Multi-center	190	Radiomics and clinical features	LR	0.72
Li et al. [108]	2020	T2WI ADC CE-T1WI CE-CT	Pre-nCRT	Retrospective Single center	118	Radiomics and clinical features	LR	0.925
Giannini et al. [109]	2019	T2WI ADC PET/CT	Pre-nCRT	Retrospective Single center	52	Radiomics features	LR	0.86

T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; T1WI, T1-weighted imaging; CE-TIWI, contrast-enhanced T1-weighted imaging; CE-CT, contrast-enhanced computed tomography; PET/CT, positron emission tomography/computed tomography; nCRT, neoadjuvant chemoradiotherapy; KNN, K-nearest neighbors; NB, naïve Bayes; RF, random forest; XGB, extreme gradient boosting; ROC curve, receiver operating characteristic curve; LR, logistic regression; SVM, support vector machine; BM, Bayesian model; EL, ensemble learning; *The AUC is from the top-preformed model of the training set.

multicenter study, Shayesteh et al. [99] combined T2WI features before and after nCRT and delta-radiomics features to develop NR prediction models with multiple classifiers; the top-performing model had an AUC of 0.96 and an accuracy of 0.93. Shayesteh et al. [99] also reported that delta-radiomics could improve the accuracy of the predictive model. Delta-radiomics may serve as an indirect marker of the subtle alterations induced by therapy, which could be essential knowledge for projecting the course of treatment. Most current studies only focus on pre-treatment images and ignore post- and delta-treatment images, which may eliminate some essential parameters and subsequently reduce the predictive power.

In a multimodal radiomics study [109], radiomics features were extracted from PET and MRI, including T2WI and ADC, for the development of PET- and MRI-based models, and MRI-PET combined models. The MRI-PET combined model achieved the best predictive efficacy with an AUC of 0.86, which demonstrated the benefit of multimodal radiomics.

4. CHALLENGES AND PROSPECTS

Radiomics is a useful tool that has demonstrated great promise in predicting therapeutic responses. A variety of excellent models have been developed using radiomics in predicting the response to treatment in LARC patients after nCRT; however, some flaws persist.

First, most studies are retrospective with small sample sizes and lack independent external validation, making it impossible to guarantee the generalizability of the developed models. Shahzadi et al. [107] designed an external validation study by selecting 11 published radiomics studies and applying the radiomics models to a multicenter cohort. Only one study performed well from this independent external dataset, indicating that radiomics studies generally lack good reproducibility and repeatability. Therefore, it is imperative to carry out additional extensive, multicenter, and prospective studies. Second, various centers have different machine settings and imaging acquisition protocols, which might affect the capacity of a model for generalization. Studies have shown that each step in the radiomics workflow, such as individual differences, scanners, acquisition protocols, and reconstruction settings, directly affect the reproducibility and accuracy of the developed radiomics models [110, 111]. Regular quality assurance checks and maintenance of the scanners can reduce the impact of differences in scanners and acquisition parameters in radiomics studies. In addition, eliminating radiomic features that are sensitive and unstable to different influencing factors can improve radiomic model robustness; however, there is also the possibility of losing important information. Third, manual delineation of the ROI by radiologists is commonly used in many studies. Due to individual preferences and diagnostic experience, the ROI delineation of the same image may vary significantly from radiologist-to-radiologist. In using automatic or semi-automatic ROI segmentation techniques, interobserver subjectivity can be somewhat mitigated. Fourth, the reproducibility of radiomics models may be hampered by unclear descriptions of the radiomics workflow, such as ambiguous criteria for tumor delineation and unclear selection of the final radiomics features. This issue might be resolved by reporting studies in accordance with the TRIPOD statement [112].

At present, the interpretability of radiomic features and models remains a challenge, which results in reservations towards the use of radiomics in clinical applications [24, 113]. In contrast, radiomics studies have used different evaluation metrics to assess the performance of developed models, such as discrimination statistics of the models (ROC curve and AUC), calibration statistics (calibration curve), and clinical utility (decision curve), which make it difficult to compare the performance between different models. Therefore, improvement in radiomic model explanation and the establishment of consistent standards for model evaluation are urgently needed for the development of radiomics. It is worth noting that combining radiomics with pathomics and genomics may improve the accuracy of the model and is also in need of further development for radiomics in the future.

5. CONCLUSION

Radiomics, as an emerging technique, has provided new perspectives and practical techniques to predict the response of patients with LARC to nCRT. However, before radiomics can be formally applied in clinical settings, radiomics must still overcome several obstacles. To confirm the true clinical value of radiomics, large-scale, multicenter, and prospective radiomics studies are required.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest.

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