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Editorial Board of *World Journal of Gastroenterology*, Andrada Seicean, MD, PhD, Professor, Regional Institute of Gastroenterology and Hepatology, University of Medicine and Pharmacy, 19-21 Croitorilor Street, Cluj-Napoca 400192, Romania. andrada.seicean@umfcluj.ro

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Role of radiomics in the diagnosis and treatment of gastrointestinal cancer

Qi Mao, Mao-Ting Zhou, Zhang-Ping Zhao, Ning Liu, Lin Yang, Xiao-Ming Zhang

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Qi Mao, Mao-Ting Zhou, Ning Liu, Lin Yang, Xiao-Ming Zhang, Department of Radiology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, Sichuan Province, China

Zhang-Ping Zhao, Department of Radiology, Panzhihua Central Hospital, Panzhihua 617000, Sichuan Province, China

Corresponding author: Lin Yang, MD, Professor, Department of Radiology, Affiliated Hospital of North Sichuan Medical College, No. 63 Wenhua Road, Nanchong 637000, Sichuan Province, China. linyangmd@163.com

Abstract

Gastrointestinal cancer (GIC) has high morbidity and mortality as one of the main causes of cancer death. Preoperative risk stratification is critical to guide patient management, but traditional imaging studies have difficulty predicting its biological behavior. The emerging field of radiomics allows the conversion of potential pathophysiological information in existing medical images that cannot be visually recognized into high-dimensional quantitative image features. Tumor lesion characterization, therapeutic response evaluation, and survival prediction can be achieved by analyzing the relationships between these features and clinical and genetic data. In recent years, the clinical application of radiomics to GIC has increased dramatically. In this editorial, we describe the latest progress in the application of radiomics to GIC and discuss the value of its potential clinical applications, as well as its limitations and future directions.

Key Words: Gastrointestinal cancer; Diagnosis; Treatment; Radiomics; Therapeutic response; Hepatocellular carcinoma

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Core Tip: In this editorial, we summarize the latest advances of radiomics in the field of gastrointestinal cancer diagnosis and treatment. Radiomics has great potential in precision treatment decision-making for gastrointestinal cancer. However, radiomics studies have had relatively marked heterogeneity in their workflow. In the future, it will be necessary to establish and promote an imaging data acquisition protocol, standardize the research workflow, and conduct multicenter prospective studies on quality control.

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INTRODUCTION

Gastrointestinal cancer (GIC) has high morbidity and mortality rates[1]. It causes approximately 5000000 new cases and 3540000 deaths worldwide each year, making it one of the main causes of cancer death[1]. Because of the high heterogeneity of these tumors, it is difficult to implement precision treatment[2]. Lambin *et al*[3] proposed the concept of radiomics in 2012. The emerging field of radiomics can convert potential pathophysiological information in existing medical images that cannot be recognized by the human eye into high-dimensional quantitative image features[2-4]. By analyzing the relationships between these features and clinical and genetic data, we can characterize tumor lesions, evaluate therapeutic responses, and predict survival. In recent years, research on the application of radiomics to GIC has grown dramatically. With this editorial, we aim to describe the latest advances of radiomics in the assessment of GIC and to explore the value of its potential clinical applications, its limitations, and its future directions.

RADIOMICS WORKFLOW

Imaging modalities that can be used for radiomics analysis include computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET). Since CT is the most commonly used staging method for esophageal cancer (EC) and gastric cancer (GC), most radiomics studies on EC and GC are based on CT images[5-9]. In contrast, as MRI is widely used for colorectal cancer (CRC) staging, most radiomics studies on CRC are based on MRI features[10-13].

The workflow of radiomics usually includes image acquisition, lesion segmentation, feature extraction and selection, model building, and validation[14]. Lesion segmentation and feature extraction are the most essential steps. Manual, automatic, and semiautomatic segmentation methods are often used to segment the region of interest (ROI) or volume of interest (VOI) (2D or 3D) in a target lesion, and manual segmentation is the most commonly used method (gold standard)[15]. After lesion segmentation, hundreds of radiomic features (shape, first-order, second-order, and higher-order radiomic features) can be extracted from the acquired image. Using all radiomic features to analyze an image will lead to overfitting; thus, feature selection is performed to reduce the number of features that are redundant and irrelevant. The best radiomic features can be selected by dimensionality reduction to improve model efficiency. After feature selection, a radiomics model must be generated. Most published studies use machine learning (ML) and deep learning (DL) methods to build classification and prediction models. Finally, the radiomics model can be validated in internal and external cohorts such that the model can be further optimized and the prediction performance can be maximized. The receiver operating characteristic (ROC) curve is the most commonly used method to evaluate model performance (Figure 1).

EC

Published studies have mainly investigated the predictive ability of radiomics in the staging, therapy response, and postoperative recurrence of EC[16-19].

Radiomic characteristics based on CT have good predictive potential for EC staging[20,21]. Yang *et al* [19] reported that CT radiomic characteristics were significantly correlated with the tumor (T) stage and tumor length of EC and showed good predictive performance for both; the area under the ROC curve (AUC), sensitivity, and specificity were 0.86, 0.77 and 0.87, respectively, and 0.95, 0.92 and 0.91. Radiomic features also have good efficacy in predicting EC lymphatic metastasis[7,22-24]. Liu *et al*[20] suggested that baseline CT texture is a biomarker for the preoperative assessment of T, lymph node (N), and overall staging of esophageal squamous cell carcinoma (ESCC). Wu *et al*[25] established a model based on the radiomic characteristics of the late arterial phase of CT, which well distinguished early (I-

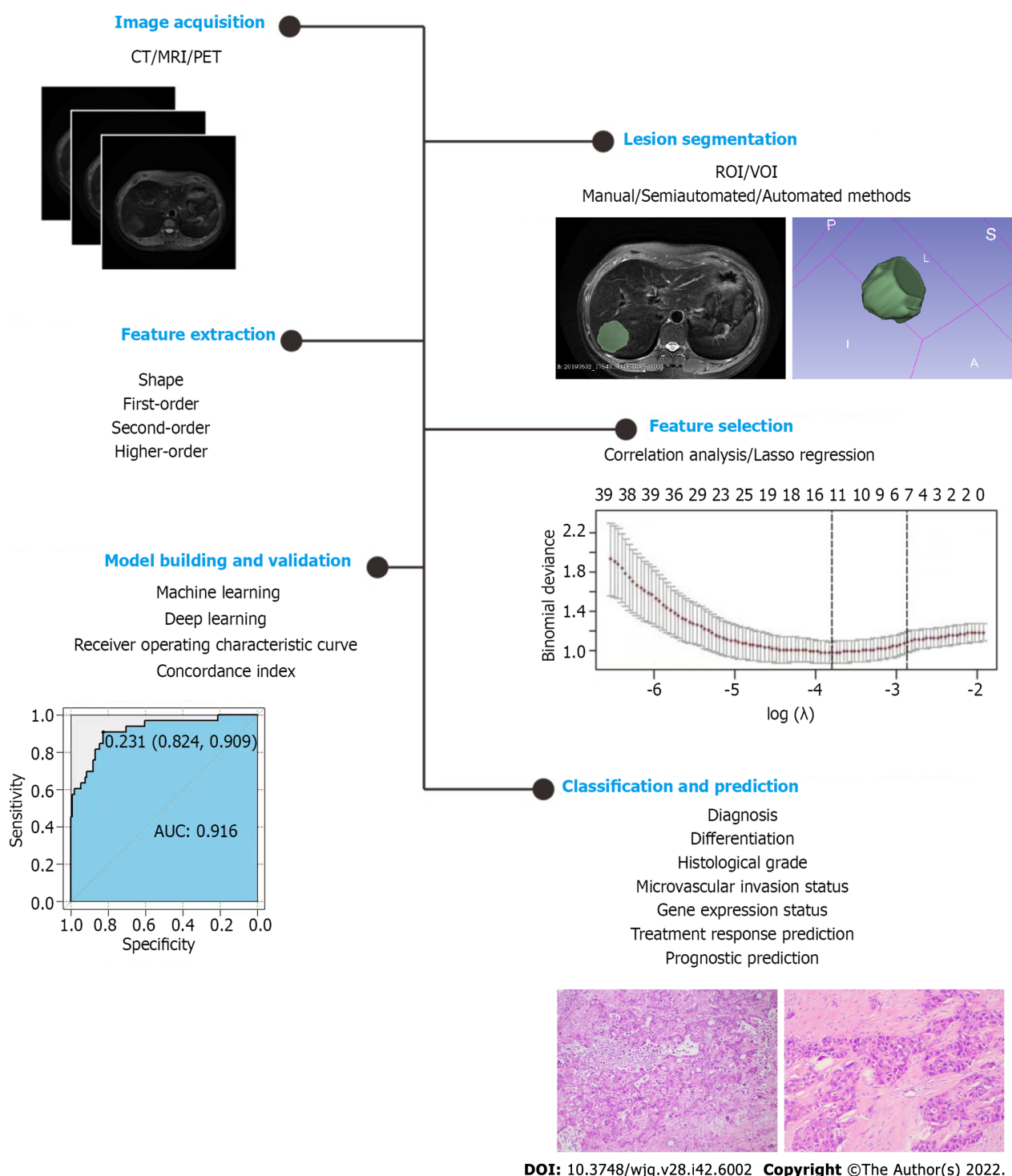


Figure 1 The framework of the proposed liver lesion classification. ROI: Region of interest; VOI: Volume of interest.

II) and late (III-IV) ESCC, and the model's efficacy was better than that of tumor volume.

Locally advanced EC often requires neoadjuvant chemoradiotherapy (NACRT)[26], whose treatment outcome is associated with tumor heterogeneity[27,28]. Radiomics can extract tumor heterogeneity data and has good application potential in improving the treatment stratification of patients. Radiomic characteristics are helpful for evaluating the response of EC to NAC or NACRT, distinguishing responders from nonresponders, for which it performs better than traditional parameters[29-32]. A prospective multicenter study[33] developed and validated a three-dimensional DL model applied to preprocessed CT images to predict the response of patients with locally advanced thoracic esophageal squamous cell carcinoma (TESCC) to concurrent chemoradiotherapy. The three-dimensional DL model achieved good predictive performance, with an AUC in the training cohort of 0.897 [95% confidence interval (CI): 0.840-0.959] and an AUC in the validation cohort of 0.833 (95%CI: 0.654-1.000). It is also feasible to use radiomics to predict the pathological complete response (pCR) of EC[34,35]. Patients with

a pCR after NACRT have a higher overall survival (OS) rate[36,37], but nonresponders will not benefit from this therapy[38]. This information can provide guidance for personalized treatment of EC patients [28]. A CT-based radiomics study showed that a model that combined the intratumoral and peritumoral radiological characteristics could improve the predictive performance of the pCR of EC NACRT. In the test set, the AUC was 0.852 (95%CI: 0.753-0.951), the accuracy was 84.3%, the sensitivity was 90.3%, and the specificity was 79.5%[35]. Several studies of radiomics based on MRI or ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET also showed its efficacy in predicting the response to EC treatment[39-42]. The application of radiomics to immunotherapy has also achieved good response prediction value[43].

Radiomics has also made progress in predicting the recurrence and prognosis of EC patients[44-47]. Tang *et al*[48] predicted the early recurrence of locally advanced ESCC after trimodal therapy based on enhanced CT radiomics. The results showed that in the training cohort, the AUCs of the radiomics model, the clinical model, and the combined model were 0.754, 0.679, and 0.821, respectively, and they were 0.646, 0.658, and 0.809 in the validation cohort; the combined model was the best. Qiu *et al*[49] developed and validated a prediction model based on radiomic features extracted from contrast-enhanced CT images to estimate the recurrence-free survival (RFS) of patients who achieved pCR through NACRT and surgery. The results showed that the radiomic characteristics were significantly correlated with RFS. In the training cohort and the validation cohort, compared with the nomograms of the radiomic characteristics and of clinical risk factors, the nomogram combining the radiomic characteristics and clinical risk factors had optimal performance. Other studies have shown that combining the radiomic characteristics of primary tumors and regional lymph nodes with clinical-pathological factors can improve OS prediction[50].

Other studies showed that CT-based radiomics features also had good predictive performance for classifying patients according to histological differentiation[51-53], the expression of programmed death-ligand 1, and CD8⁺ tumor-infiltrating lymphocytes of EC[5].

GC

In recent years, some researchers have also explored the value of radiomics to the diagnosis and treatment of GC[9,54,55]. The CT radiomics model has high application value in the identification of GC [54,56-58]. Feng *et al*[59] used a transfer learning radiomics nomogram (TLRN) with whole-slide images of GC as the source domain data to distinguish Borrmann type IV GC from primary gastric lymphoma before surgery. The TLRN that integrated transfer learning radiomics signatures (TLRS), clinical factors, and CT subjective findings was developed through multiple logistic regression (LR). The results showed that the TLRN performed better than the clinical model and the TLRS. The AUCs of the internal and two external validation cohorts were 0.958 (95%CI: 0.883-0.991), 0.867 (95%CI: 0.794-0.922), and 0.921 (95%CI: 0.860-0.960), respectively[59]. Wang *et al*[60] reported that a DL radiomics model based on CT images had a potential role in the T staging of GC. For distinguishing T2 from T3/4 tumors, the AUCs of the arterial phase-based radiomics model in the training group and the test group were 0.899 (95%CI: 0.812-0.955) and 0.825 (95%CI: 0.718-0.904), respectively. The AUC of the radiomics model based on the portal vein phase in the training and testing cohorts was 0.843 (95%CI: 0.746-0.914) and 0.818 (95%CI: 0.711-0.899), respectively[60]. An important factor in the failure of GC treatment is lymph node metastasis (LNM) and cancer spread in the peritoneal cavity[61]. In GC, the most common metastatic sites are the distant lymph nodes (56%), liver (53%), and peritoneum (51%)[62]. Accurate assessment of LNM and preoperative N staging is critical for the accurate treatment of GC patients. Most studies have shown that CT-based radiomics models have good accuracy in predicting early GC lymph node and peritoneal metastasis before surgery[63-66]. A ML model based on preoperative ¹⁸F-FDG-PET/CT obtained similarly good results[67].

CT-based radiomic characteristics also perform well in predicting the response to NAC and radiotherapy in patients with advanced GC[68-71]. Jiang *et al*[72] showed that a DL CT signature could help to identify patients who might benefit from adjuvant chemotherapy for GC and improve prognostic prediction. A radiomics study based on ¹⁸F-FDG-PET signatures obtained similar results[73]. In addition, radiomics can be used to predict the histological grade of GC before surgery[74] and is useful for GC classification[75,76].

CRC

The application of radiomics to CRC has mainly focused on the evaluation of stage, neoadjuvant therapy outcome, and gene mutations[77,78].

Radiomics models are helpful for CRC staging[79-81]. LNM is an independent risk factor affecting the prognosis of CRC patients. Radiomics models can effectively predict LNM in CRC patients before surgery[82-85]. Liu *et al*[84] found that multiregional-based MRI radiomics combined with clinical data could improve the efficacy of predicting LNM. He *et al*[85] developed and tested five ML models based on the radiomic features of F-18-FDG-PET/CT and PET for their preoperative prediction of LNM in the CRC region: LR, support vector machine, random forest (RF), neural network, and extreme gradient boosting. The results showed that the LR (AUC 0.866, 95%CI: 0.808-0.925) and extreme gradient boosting models (AUC 0.903, 95%CI: 0.855-0.951) performed the best, outperforming F-18-FDG-PET/CT on both the training set and the test set[85]. Other studies have also shown that radiomics has a good ability to predict metastasis to distant organs, such as the liver and lung, as well as vascular and

perineural invasion[86,87]. It is reported that the predictive power of CT-based radiomics for the preoperative staging of CRC. The results showed that the radiomic features were an independent predictor of CRC staging. CRC was successfully divided into stages I-II and III-IV in the training and validation datasets. The AUC in the training dataset was 0.792 (95%CI: 0.741-0.853), the sensitivity was 0.629, and the specificity was 0.874. The AUC in the validation dataset was 0.708 (95%CI: 0.698-0.718), the sensitivity was 0.611, and the specificity was 0.680[79].

Radiomics models have had excellent performance in noninvasively predicting the response to NAC and NACRT in patients with locally advanced CRC (including liver metastasis)[88-91]. They have also achieved good efficacy in predicting the response to CRC targeted therapy[77,92].

Mutations in the *KRAS*, *NRAS*, or *BRAF* gene indicate that CRC patients will lack a response to drugs targeting epidermal growth factor receptor. In 2016, the National Comprehensive Cancer Network guidelines recommended that all patients with suspected or confirmed metastatic CRC should be tested for *KRAS*/*NRAS*/*BRAF* mutations, but this requires pathological tissue specimens. It is gratifying that some radiogenomics studies have shown that the radiomic characteristics of CT and MRI may help to predict the genotype of CRC tumors before surgery[93-95]. Yang *et al*[96] reported that CT radiomic characteristics were associated with *KRAS*/*NRAS*/*BRAF* mutations. Another MRI radiomics study found a good correlation between quantitative features and gene mutations, while there was no correlation between qualitative features and gene mutations[97].

More recent studies have shown that radiomics can predict CRC histological grade before surgery[98, 99].

LIVER CANCER

The application of radiomics to hepatocellular carcinoma (HCC) involves differential diagnosis, determination of microvascular invasion (MVI) status, histological grade, gene expression status, and treatment response, and prognostic prediction[100-104].

Because HCC has a typical enhancement mode, dynamic contrast-enhanced CT, MRI, and ultrasound have played major roles in the diagnosis and differentiation of HCC[105-107]. However, it is sometimes difficult to distinguish some small nodules from atypical lesions[108-111]. Radiomics can achieve quantitative analysis of tumor biological behavior and heterogeneity, helping identify liver nodules[112-114]. Yasaka *et al*[115] investigated the performance of a DL method to distinguish liver masses on dynamic enhanced CT. There are five types of these masses: Type A, classic HCC; type B, malignant liver tumors other than HCC; type C, indeterminate masses or mass-like lesions, plus rare benign liver masses other than hemangiomas and cysts; type D, hemangiomas; type E, cysts. The median accuracy of the mass identification on the test set was 0.84. The AUC that distinguished the types A-B from types C-E was 0.92. Hamm *et al*[116] used a DL method to classify common liver lesions with typical imaging characteristics on multiphasic MRI, including a total of 494 liver lesions from six categories, which were divided into training ($n = 434$) and test groups ($n = 60$). Their DL system had an accuracy of 92%, a sensitivity of 92%, and a specificity of 98%. For HCC classification, the true-positive rate and false-positive rate were 93.5% and 1.6%, respectively, and the AUC was 0.992[116]. Other studies have reached similar conclusions[108,110].

The 5-year recurrence rate of HCC resection can reach 70%[103]. Pathological features such as histological grade and MVI of HCC were significantly correlated with postoperative recurrence and prognosis[117-120]. Histological grade, MVI status[121-125], and gene expression[113,126,127] in HCC can be successfully predicted by radiomics models before surgery. An MRI-based radiomics study showed that the AUCs of the MVI nomogram in the validation cohort using the RF algorithm and LR analysis were 0.920 (95%CI: 0.861-0.979) and 0.879 (95%CI: 0.820-0.938), respectively[123].

Radiomics models based on contrast-enhanced CT and MRI can predict the response of middle- and late-stage HCC to local treatment and systemic treatment[10,128-130] and the early recurrence and the prognosis after HCC resection[101,102,131,132]. Zhang *et al*[133] evaluated the effectiveness of predicting OS after HCC resection based on contrast-enhanced MR imaging features. The results showed that preoperative clinical features and semantic imaging features were significantly correlated with the survival rate; the combined model had the best predictive performance[133].

Some studies using radiomics to predict the occurrence of CRC liver metastases are particularly interesting[134-137]. Rao *et al*[137] retrospectively analyzed the primary staging CT data of 29 CRC patients. The patients were divided into three groups: The non-liver-metastasis group, the simultaneous liver metastasis (LM) group, and the metachronous LM group within 18 mo. Whole-liver texture analysis was performed on the liver parenchyma that was clearly disease-free on the portal vein image. The results showed that compared with those in nonmetastatic patients, the mean entropy 1.5 (E1.5) and E2.5 values of the whole liver in patients with synchronous metastasis were significantly increased, and the uniformity 1.5 (U1.5) and U2.5 values were significantly decreased. The AUCs for the diagnosis of synchronous metastasis based on E1.5, E2.5, U1.5, and U2.5 were 0.73-0.78[137]. Beckers *et al*[138] conducted a similar retrospective multicenter study. They included a total of 165 cases of CRC, which were also divided into the nonmetastasis group, the synchronous metastasis group, and the metastasis

group (within 24 mo). Univariate analysis confirmed that U, sex, tumor site, nodal stage, and carcinoembryonic antigen (CEA) were potential predictive factors; multivariate analysis showed that U was still a factor predicting early metastasis; and none of the parameters could predict intermediate/late metastasis[138]. Other studies have shown no significant difference in CT texture parameters of liver parenchyma between CRC patients with and without liver metastasis[134,135]. The conclusions of these studies are inconsistent, so the prediction of LM of CRC based on the texture characteristics of the liver parenchyma requires further study. Recently, Liet *al*[139] investigated the efficacy of a radiomics model based on baseline CRC contrast-enhanced CT in predicting metachronous liver metastases in CRC patients. The AUC of the radiomics feature model was 0.78 ± 0.07 , and the AUC of the clinical feature model was 0.79 ± 0.08 . The model combining the two performed best, with AUCs of 0.79 ± 0.08 and 0.72 ± 0.07 in the internal and external validation cohorts, respectively. They believed that the radiomic characteristics of primary CRC lesions are often affected by fewer factors and are more stable; their radiomic characteristics have the potential to distinguish patients at risk of liver metastasis.

PANCREATIC CANCER (PC)

For PC, the application of radiomics mainly focuses on identification, treatment response prediction, and prognostic prediction[140-142]. Many studies have focused on the diagnosis and differentiation of pancreatic ductal adenocarcinoma (PDAC)[143-146]. Chu *et al*[146] investigated the utility of CT radiomics in distinguishing PDAC from normal pancreas. In their retrospective case-control study, 190 PDAC patients and 190 healthy potential renal donors were included. The overall accuracy of RF binary classification was 99.2%, with an AUC of 99.9%; all PDAC cases were correctly classified. Park *et al*[145] confirmed that CT-based ML of radiomics features was helpful to distinguish between autoimmune pancreatitis and PDAC, with an overall accuracy of 95.2%. The radiomics model based on PET/CT also showed good performance in distinguishing benign autoimmune pancreatitis from malignant PDAC lesions[143,144].

Other studies have shown that radiomics can better predict the treatment response and prognosis of PC[142,147]. Simpson *et al*[141] evaluated the potential of MRI-based radiomics to predict the response to PC treatment. A total of 20 patients with unresected nonmetastatic PDAC were enrolled, all of whom received NAC followed by five rounds of MR-guided stereotactic body radiotherapy. Half of the 20 patients were defined as having histopathological tumor regression or tumor response based on an enhanced CT. The AUC of the model based on the RF algorithm was 0.81 (95%CI: 0.594-1.000); the adaptive least absolute shrinkage and selection operator (LASSO) algorithm achieved AUC of 0.81 (95%CI: 0.596-1.000). Xie *et al*[148] used a CT-based radiomics nomogram to predict the survival of patients with resected PDAC. The radiomics score developed based on CT imaging features was significantly correlated with disease-free survival (DFS) and OS in patients with PDAC. The radiomics nomogram showed good discrimination in both the training cohort and the validation cohort, being superior to the clinical model and the TNM staging system for survival estimation. The model integrating the radiomics score and clinical data had the best predictive performance, but there was no correlation between the radiomics score and recurrence pattern. Similar results were seen by Healy *et al* [149].

LIMITATIONS AND FUTURE DIRECTIONS

In this editorial, we summarize the results of the application of radiomics to the field of GIC diagnosis and treatment. These results show that radiomics has great potential for decision-making about precision treatments for GIC. Moreover, these results have important reference value for studies of other systemic tumors.

However, some limitations to the clinical application of radiomics remain[150,151]. The first key challenge is the use of different imaging techniques by different institutions and/or scanners. To ensure that the academic community can obtain high-quality radiological data resources, it is necessary to establish and promote certain imaging acquisition protocols[149]. Second, the current research uses different software and different feature selection methods, focuses on different feature sets, and applies different statistical and bioinformatic methods for data analysis and interpretation, which limit the reproducibility of radiomics models[152,153]. Future research workflows need to be standardized. Third, many relevant radiomics studies employ single-center retrospective datasets. A quality-controlled multicenter prospective study plan is ideal. In addition, the evidence level rating reflects the feasibility of incorporating radiomics research into clinical practice. Recently published guidelines and checklists aiming to improve the quality of radiomics studies, including the radiomics quality score, modified Quality Assessment of Diagnostic Accuracy Studies tool, image biomarker standardization initiative guideline, and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis checklist, have been applied to radiomics evaluations[154-157]. These studies have shown that the current scientific and reporting quality of many radiomics studies is insufficient;

feature reproducibility, open science categories, and clinical utility analyses need to be improved; and study objectives, blinding, sample sizes, and missing data must be reported[154-157]. In the future, radiomics studies should adhere to these guidelines to facilitate the translation of radiomics research into clinical practice[156].

CONCLUSION

Radiomics has great potential in precision treatment decision-making for gastrointestinal cancer. However, radiomics studies have had relatively marked heterogeneity in their workflow. In the future, it will be necessary to establish and promote an imaging data acquisition protocol, standardize the research workflow, and conduct multicenter prospective studies on quality control. In addition, the combination of radiomics with multiomics may lead to a major breakthrough in individualized medical treatment of tumors.

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Country/Territory of origin: China

ORCID number: Qi Mao 0000-0003-1301-069X; Mao-Ting Zhou 0000-0003-2034-2086; Zhang-Ping Zhao 0000-0001-7150-161X; Ning Liu 0000-0003-3587-5440; Lin Yang 0000-0001-8746-9255; Xiao-Ming Zhang 0000-0001-5327-8506.

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