

Radiomics approaches in gastric cancer: a frontier in clinical decision making

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Abstract

Objective: To review the application of radiomics in gastric cancer and its challenges as well as future prospects.

Data sources: A research for relevant studies were performed in PubMed with the terms of “radiomics,” “texture analysis,” and “gastric cancer.” The search was updated until February 28th, 2019.

Study selection: All original articles regarding the investigation of texture analysis or radiomics in gastric cancer were retrieved. Only papers written in English were included.

Results: A total of 17 original articles were selected in final. It is shown that radiomics has yielded moderate to excellent performance in a spectrum of respects including differential diagnosis, assessment of histological differential degree, evaluation of tumor stage, prediction of response to therapy, and prognosis in gastric cancer. Yet, a number of challenges are facing both radiomics itself and its application in gastric cancer.

Conclusions: Radiomics holds great potential in facilitating decision-making in gastric cancer. With the standardization of workflow and advancement of machine learning methods, radiomics is expected to make great breakthroughs in precision medicine of gastric cancer.

Keywords: Gastric cancer; Radiology; Radiomics

Introduction

Gastric cancer is a major health burden, although its incidence has decreased worldwide in recent decades. It still serves as the third leading cause of malignancy-related death worldwide. It is estimated that there were over 1,000,000 new gastric cancer cases and about 783,000 gastric cancer deaths globally in 2018.^[1] In China, the reported new gastric cancer cases and deaths were respectively 6,791,000 and 498,000 patients in 2015.^[2] Imaging modalities play a crucial role in the diagnosis, staging, and risk stratification of gastric cancer for optimal therapeutic strategy selection and outcome improvement.^[3] Radiomics is an emerging field using a non-invasive approach to extract numerous quantitative features from medical images, especially parameters not visible to the naked human eye or quantifiable by routine analysis.^[4-6] Radiomics has shown promise for gene expression, pathological classification, tumor metastasis, treatment response, and clinical outcomes in variable cancers, such as lung cancer, breast cancer, rectal cancer, hepatocellular carcinoma, nasopharyngeal carcinoma,

bladder cancer, and gastric cancer.^[7-17] This article briefly reviews the application of radiomics in gastric cancer and challenges as well as future prospects.

Overview of Radiomics

The concept of radiomics was raised by Lambin *et al*^[18] in 2012 and subsequently refined by Kumar *et al*^[19] as the high-throughput extraction and analysis of large amounts of advanced quantitative imaging features from medical images obtained with computed tomography (CT), positron emission tomography (PET) or magnetic resonance imaging. The dominant advantage of radiomics is that it enables the acquisition of numerable quantitative features which could offer information on tumor phenotype and microenvironment which is unavailable by traditional radiology.^[5,18] Another major strength of radiomics is the utilization of artificial intelligence or machine learning approaches, which will transform the mineable high-dimensional data to develop diagnostic, predictive or prognostic radiomic models or signatures to support personalized clinical decision making.^[4,20]

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A radiomics study can be structured into the following four phases: (1) Image acquisition: obtaining large-scale medical images with standard scanning and reconstruction protocols is pivotal for eliminating unnecessary confounding variability in radiomics; (2) Image segmentation: regions of interest (ROIs) or volumes of interest (VOIs) of the tumor, metastatic lesions, and normal tissues can be segmented manually or semi-automatically for further analysis; (3) Feature extraction and selection: high-throughput extraction of quantitative imaging features from ROIs or VOIs is the essence of radiomics. Commonly used radiomics features can be categorized into shape and size features, first-order histograms, second-order histograms (textural), and fractal features.^[6,21] Features that are redundant or may not correlated with the given tasks should be excluded for model construction. The least absolute shrinkage and selection operator (LASSO), maximum relevance and minimum redundancy, and principal component analysis are frequently used feature selection methods; (4) Model construction and validation: identification of optimal machine-learning models based on the clinical information and selected features is the pivotal step. Support vector machine (SVM), random forest, artificial neural networks (ANNs) and bootstrapping are widely used machine-learning methods. The selected model should be validated prior to its application in scientific and clinical communities. Excellent models should exhibit statistical consistency between the training and validation sets.^[5,6,19,21]

Application of Radiomics Approaches in Gastric Cancer

Data sources, study selection, and analysis

A research for relevant studies was performed in PubMed databases with index terms of “radiomics,” “texture analysis,” and “gastric cancer.” The search was updated until February 28th, 2019. All original articles regarding the investigation of texture analysis or radiomics in gastric cancer were retrieved. Only papers written in English were included. A total of 17 studies were selected in final. These investigations have found that radiomics may be attributable to the differential diagnosis (two studies), assessment of histological differential degree (two studies), pathological N stage (three studies), M stage (occult peritoneal metastasis, one study), vascular invasion (one study), response to chemotherapy (five studies) or radiotherapy (one study), and prognosis of surgery (two studies). A summary of these works was presented in Table 1.

Differential diagnosis

Primary gastric lymphoma, gastrointestinal stromal tumor, and adenocarcinoma can frequently mimic each other, yet with remarkably different management strategies and prognoses.^[22] The differential diagnosis remains challenging based on routine CT characteristics. Two studies have investigated the ability of radiomics for differential diagnosis of gastric cancer. Quantitative radiomics analysis is shown to be promise to supplement conventional CT in the distinction of gastric cancer. The work conducted by Ba-Ssalamach *et al*^[22] analyzed the

texture features derived from pre-operative arterial phase (47 patients) and portal phase (48 patients) images. They found that VOI-based texture features from arterial phase CT images can differentiate gastrointestinal stromal tumor from lymphoma with 100% accuracy and can distinguish adenocarcinoma from lymphoma with a misclassification rate of 3.1%; the corresponding misclassification rate was 8% and 10% based on portal phase images, respectively. Ma *et al*^[23] collected the pre-operative portal phase images of 40 patients with Bormann IV type gastric cancer and 30 cases with gastric lymphoma to carry out radiomics analysis, and they reported that whole-lesion-based texture features from portal phase CT images can differentiate adenocarcinoma from lymphoma with an accuracy of 87%.

Prediction of histological grade

The histopathological features of gastric cancer significantly influences treatment and prognosis of patients.^[24] Two studies have been performed to explore the values of radiomics in the assessment of histological grade of gastric cancer. The study by Liu *et al*^[25] segmented the whole lesions on the pre-operative arterial and portal phase images of 107 patients. They identified that the radiomic features were correlated with the histological grade ($r = -0.231$ to -0.324) and Lauren type ($r = 0.228-0.321$). Apparent diffusion coefficient (ADC) maps of 78 patients were collected by Zhang *et al*^[26] and the whole lesions were segmented. The extracted histogram parameters were found to be significantly different in lesions with disparate histological grades. Nevertheless, the role of these histogram parameters is likely to be limited in clinical practice because the area under the curve (AUC) was less than 70%.

Prediction of tumor stage

The accurate evaluation of tumor stage is a pre-requisite for the selection of an appropriate therapeutic approach and have prognostic significance.^[24] Altogether five studies were carried out to evaluate the role of radiomics in the prediction of lymph node status, vascular invasion, and occult peritoneal metastasis. Traditional method to evaluate the lymph node is based on the size of the lymph node. Diagnostic uncertainty frequently occurs as normal-size nodes can be malignant yet inflammatory nodes may be enlarged. The radiomics approach was shown to be promising in assessment of tumor stage. Liu *et al*^[27,28] segmented the VOIs of lesions on ADC maps in approximately 80 cases and found that whole-lesion-based radiomic features can identify patients with positive lymph node metastases with an accuracy ranging between 74% and 81%, but these signatures were not capable to predict the T stage. Liu *et al*^[29] evaluated the whole-volume ADC-based entropy parameters in the pre-operative assessment of gastric cancer's aggressiveness in 64 patients. They found that four entropy related parameters were obviously differed between patients with and without perineural invasion. Feng *et al*^[30] collected the pre-operative portal phase images of 490 patients. A total of 93 features were derived from the segmented ROIs. A radiomics model was built using the modified recursive

Table 1: Radiomics study in gastric cancer.

Purpose	Author	Year	Study type	Sample size	Image acquisition	Image type	Segmentation	Features extracted	Statistical analysis	Validation	Results
Differential diagnosis	Ba-Salahmah <i>et al.</i> ^[22]	2013	Retrospective	67 (AP), 73 (PP)	Single center, 4 CT scanners	Pre-treatment AP and PP CT	ROI	First order statistics; Second order GLCM, RLM statistics; Wavelet transformed statistics	Misclassification rate	-	Arterial phase: accurately differentiate GIST from lymphoma, highly successful in the differentiate between adenocarcinoma and lymphoma with a misclassification rate of 3.1%. Portal phase: differentiate GIST from lymphoma; 8% adenocarcinoma from GIST with a misclassification rate of 10%. Differentiate adenocarcinoma from lymphoma: AUC:0.86; Sensitivity:70%; Specificity: 100%; Accuracy: 87%
Differential diagnosis	Ma <i>et al.</i> ^[23]	2017	Retrospective	70	Single center, 2 CT scanners	Pre-treatment PP CT	VOI	Shape and size based features, First order statistics; texture features, wavelet features	ROC, AUC	-	Radiomics features were correlated with histological differentiation degree ($r = -0.231$ to 0.324) and Lauren type ($r = 0.228-0.321$). Significant difference was identified in ADC histogram parameters between different histological grades, however AUC <0.7
Histological grade	Liu <i>et al.</i> ^[25]	2017	Retrospective	107	Single center, 2 CT scanners	Pre-treatment contrast AP and PP CT	ROI	First order statistics	ROC, AUC	-	Distinguish node positive from node negative by percentile ADC ₁₀ : AUC: 0.79; sensitivity: 72%; specificity: 81%; accuracy: 74%; Not feasible to differential T stage
Histological grade	Zhang <i>et al.</i> ^[26]	2017	Retrospective	78	Single center, 1MRI scanner	Pre-treatment MRI-ADC map	VOI	First order statistics	ROC, AUC	-	Distinguish node positive from node negative: sensitivity: 76%; specificity: 81%, AUC:0.8
T stage, N stage	Liu <i>et al.</i> ^[27]	2017	Prospective	80	Single center, 1 MRI scanner	Pre-treatment MRI-ADC map	VOI	First order statistics	ROC, AUC	-	Differentiate positive vascular invasion by first-order entropy, sensitivity 86%, specificity 75%, accuracy: 81%, AUC: 0.82
N stage	Liu <i>et al.</i> ^[28]	2017	Prospective	87	Single center, 1 MRI scanner	Pre-treatment MRI-ADC map	VOI	First order statistics	ROC, AUC	-	The radiomics model can differentiate node positive cases with an AUC of 0.824 in the training cohort and 0.764 in the testing cohort
Vascular invasion	Liu <i>et al.</i> ^[29]	2018	Retrospective	64	Single center, 1 MRI scanner	Pre-treatment MRI-ADC map	VOI	First order statistics, Second order GLCM statistics	ROC, AUC	-	CT radiomics nomogram had an excellent accuracy for prediction of occult peritoneal metastasis (AUCs of 0.958, 0.941, 0.928, 0.920 in the training set and one internal and two external validation set)
N stage	Feng <i>et al.</i> ^[30]	2019	Retrospective	490	1 CT scanner	Pre-operative PP CT	ROI	First order statistics, Second order GLCM statistics	ROC, AUC	Internal validation	Entropy and compactness are higher in responders and uniformity is lower in responders Log OR: 3.67-4.57.
Occult peritoneal metastasis	Dong <i>et al.</i> ^[31]	2019	Retrospective	554	Multi-center (4 centers), several scanners	Pre-treatment PP CT	ROI	3D shape and size features, First order statistics, Second order GLCM and RLM statistics,	ROC, AUC, Net reclassification index, DeLong test, Hosmer-Lemeshow test	Internal and external validation	
Response to chemotherapy	Giganti <i>et al.</i> ^[32]	2017	Retrospective	34	Single center, 1 CT scanner	Pre-treatment AP CT	VOI	3D shape and size features; First order statistics, Second order GLCM and RLM statistics,	Multivariable logistic model	-	
Prognosis of curative resection	Giganti <i>et al.</i> ^[31]	2017	Retrospective	56	Single center, 1 CT scanner	Pre-treatment AP CT	VOI	First order statistics, Second order GLCM and RLM statistics	Kaplan-Meier survival analysis, Multi-variable Cox analysis	-	Energy, entropy, skewness are associated with poor prognosis, Log RR ranged 3.25-5.96 and -4.22 to -2.66.
Prognosis of curative resection	Li <i>et al.</i> ^[17]	2018	Retrospective	181	Single center, 1 CT scanner	Pre-treatment PP CT	ROV, VOI	First order statistics, Second order GLCM and RLM statistics	Two-sample <i>t</i> test, Wilcoxon rank-sum test, Pearson's chi-square test, Fisher exact test, Kaplan-Meier survival analysis	Internal validation	The CT radiomics nomogram incorporated with the radiomics signature and clinical parameters provided better predictive accuracy for prognosis of radical resection that either the radiomics signatures (Harrell concordance index: 0.82 vs. 0.71) or clinical parameters (Harrell concordance index: 0.82 vs. 0.74).
Response to neoadjuvant chemotherapy	Li <i>et al.</i> ^[33]	2018	Retrospective	30	Single center, 1 CT scanner	Pre-treatment contrast CT arterial and portal phase	VOI	First order statistics; Shape and size based features, texture features, wavelet features	T-test, Mann-Whitney-Wilcoxon test	-	It is possible to predict non-responders in locally advanced gastric cancers based on the radiomics of CT, the best model yielded an AUC of 0.722 ± 0.108
Response to chemotherapy, prognostic prediction	Jiang <i>et al.</i> ^[6]	2018	Retrospective	1591	Multi-center (3 centers), Several scanners	Pre-treatment PP CT	ROI	Radiomics signatures consisted of a combine of 19 selected features	χ^2 test, Fish exact test, Kaplan-Meier, log-rank test, Cox proportional hazards model	External validation	The radiomics signatures is superior in the prediction of patients who may benefit from chemotherapy. The HR in the prediction of DFS were 2.98, 3.17, 2.671 in the training set, internal set, and external set, and 3.72, 3.415, 2.830 in the prediction of OS
Response to chemotherapy, prognostic prediction	Jiang <i>et al.</i> ^[34]	2018	Retrospective	214	Single center, 1 PET/CT scanner	Pre-treatment PET/CT	VOI	First order statistics; Second order GLCM and RLM, NGTDM, GLSZM statistics	Kaplan-Meier, Log-rank test, Decision curve analysis	Internal validation	The radiomics signature is a powerful predictor of OS and DFS; it also could predict response to chemotherapy. The HR were 3.303 and 4.357 respectively in the training and testing cohort in the prediction of DFS, 3.354 and 2.398 in the prediction of OS.
Response and prognostification to Trazuzumab-based chemotherapy	Yoon <i>et al.</i> ^[5]	2016	Retrospective	26	Single center, 3 CT scanners	Pre-treatment PP CT	ROI	First order statistics, Second order GLCM statistics	ROC, AUC, Kaplan-Meier	-	Lower contrast, variance, higher correlation are associated with poorer survival with AUC of 0.77, 0.75, 0.77, respectively
Response to radiotherapy	Hou <i>et al.</i> ^[36]	2018	Retrospective	43	Single center, 1 CT scanner	Pre-treatment AP CT	VOI	First order statistics, Second order GLCM and RLM, NGTDM, GLSZM statistics	ROC, AUC	Internal validation	Radiomics signatures can predict the response to radiotherapy with AUCs range from 0.686 to 0.728

AP: Arterial phase; PP: Portal phase; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission imaging; ADC: Apparent diffusion coefficient; ROI: Region of interest; GLCM: Gray-level co-occurrence matrix; RLM: gray-level run-length; NGTDM: Neighborhood gray-tone difference matrix; GLSZM: Gray-level size zone matrix; ROC: Receiver operating characteristics; AUC: Area under the curve; -: Non available; GIST: Gastrointestinal stromal tumor; Log OR: Logistic odds ratio; Log RR: Logarithm of relative risk; HR: Hazards ratio; DFS: Disease free survival; k-NN: k nearest-neighbor classification; LDA: Linear discriminant analysis.

feature selection SVM method, which yielded an AUC of 0.824 in the training cohort and 0.764 in the test cohort in prediction of lymph node metastasis. Early detection of peritoneal metastasis is pivotal for optimal treatment selection and avoidance of unnecessary surgical procedures. However, the specificity of conventional CT in the detection of peritoneal metastasis is unsatisfactory only around 50%. Dong *et al*^[15] carried out a multi-center study in which 554 subjects with occult peritoneal metastasis were retrospectively analyzed. ROIs of both the tumor and the peritoneal region nearest to the center of the primary tumor were segmented. A total of 133 features were extracted on each ROI of each patient. A nomogram was constructed incorporating radiomics features extracted from the tumor and the peritoneal region as well as clinical factors. The nomogram yielded an excellent performance in the prediction of occult peritoneal metastasis with an AUC of 0.958 in the training set and 0.941, 0.928, and 0.920 in an internal and two external validation sets.

Prediction of response to therapy and patient prognosis

The identification of pre-therapeutic predictive markers for response and prognosis would be invaluable in individualized patient treatment.

Prognosis of surgical resection

Tumor-node-metastasis staging systems are primary prognostic factors, yet it is not uncommon that patients with same stage exhibit heterogeneous outcomes. Two studies evaluated the values of radiomics in the prediction of prognosis after surgical resection. Giganti *et al*^[31] investigated the association between CT texture-derived parameters and the overall survival (OS) in 56 patients with resectable gastric cancer. In total, 107 features were extracted from each ROI on pre-operative arterial phase images. The study identified that features including energy, entropy, maximum Hounsfield unit value, skewness, root mean square, and mean absolute deviation were significantly associated with a negative prognosis with logistic relative risk ranged 3.25 to 5.96 and -4.22 to -2.66. The work carried out by Li *et al*^[17] included pre-operative portal phase CT images of 181 patients. They segmented both the ROI and VOI of the tumor with the purpose to compare the performance between two-dimensional and three-dimensional segmentation. A total of 273 features were extracted from each ROI and 485 features were extracted from each VOI. LASSO method was used for feature selection and a LASSO Cox regression model was built for the prediction of OS. Both two-dimensional and three-dimensional features were associated with OS in the training set; however, no significant association for prediction of OS was found by three-dimensional features in the test set. A nomogram incorporated with the ROI-based radiomics signature and clinical parameters was built which provided better predictive accuracy for prognosis of radical resection than either the radiomics signatures (Harrel concordance index 0.82 *vs.* 0.71) or clinical parameters (Harrell concordance index 0.82 *vs.* 0.74).

Prognosis of neoadjuvant chemotherapy (NAC)

NAC is the mainstay for locally advanced cases, as it can facilitate downgrading of the lesion and improve the radical resection rate. However, not all patients could benefit from the schemes. Individuals who were insensitive to NAC may experience unnecessary drug-toxicity. Four studies were published regarding the value of radiomics in the prediction of response and prognosis of NAC until now, the results of which indicated that radiomics may provide incremental values in selection of appropriate candidates for NAC. Giganti *et al*^[32] included the pre-treatment arterial phase images of 43 patients and manually segmented the whole tumor. They found that 14 features were significantly different between the responders and non-responders at univariate analysis. Multivariate analysis revealed that entropy, range, root mean square were independent predictors of responders and non-responders with logistic odds ratio of 4.11, 3.67, and 4.57, respectively. In another study with inclusion of the pre-treatment arterial and portal phase images of 30 patients, Li *et al*^[33] analyzed the values of ROI-based radiomics features with 32 combinations of feature selection and machine-learning methods. A total of 19,985 radiomics features were extracted in the arterial and portal phase images of each patient. One machine-learning method showed AUC >0.6 using features from arterial phase images and 12 algorithms displayed AUCs >0.6 based on features from portal phase images in predicting the response to NAC. The largest study was carried out by Jiang *et al*^[16] which was a multi-center retrospective analysis with inclusion of the pre-operative portal phase CT images of 1591 patients. A total of 269 features were extracted from each ROI. A LASSO Cox regression model was used to build a prognostic classifier and 19 potential predictors were selected. The study revealed that the nomogram based on the combination of clinical factors and radiomics signatures would facilitate the prediction of disease-free survival (DFS) with hazard ratios (HRs) of 2.98, 3.17, and 2.671 in the training set, internal test set, and external test set, while the corresponding HRs for predicting OS were 3.72, 3.415, and 2.830, respectively. Additionally, a multi-center study included PET-CT images of 214 patients was conducted by Jiang *et al*^[34] Each ROI derived 80 features. A multiple-feature-based radiomics signature was constructed for predicting DFS. A nomogram was built based on the radiomics signature and clinical predictors which were shown to be a powerful predictor of OS (HRs were 3.354 and 2.398 in the training set and test set, respectively) and DFS (HRs were 3.303 and 4.357 in the training and test sets, respectively).

Prognosis of targeted chemotherapy with trastuzumab

Although a survival gain was observed for targeted therapy with trastuzumab in patients with human epidermal receptor 2 (HER2) over-expression, there are still patients who are insensitive to this approach. There has been only one study regarding radiomics in the prediction of targeted chemotherapy with trastuzumab, which was conducted by Yoon *et al*^[35] They enrolled 26 cases with HER2

over-expression aimed at predicting the response to trastuzumab treatment. A number of histogram and gray-level co-occurrence matrices (GLCM) features were derived from the manually delineated ROIs on portal phase CT images. It is reported that GLCM features including angular second moment, contrast, variance, and correlation can differentiate responders from non-responders with AUCs ranging from 0.75 to 0.77. The results supported that radiomics markers may provide additional prognostic information for patient selection.

Prognosis of radiotherapy

Radiotherapy has been proved as effective treatment strategy across a range of cancer, including gastric cancer. Nevertheless, the response to radiotherapy is highly individual.^[35] Cases received yet insensitive to radiotherapy may lead to a delay of the modification of treatment plan. The works investigated the value of radiomics in the differentiation between responder and non-responders to radiotherapy were rare. Only Hou *et al*^[36] segmented the VOIs of the pre-treatment arterial phase images of 43 patients. A total of 1117 features were extracted from each VOI. The study revealed that these signatures can predict the response to radiotherapy with AUCs of 0.714 and 0.749 using the ANN and k-nearest neighbor methods in the training set, respectively; the AUCs in the validation set were both 0.816. The study suggested that radiomics may serve as a valuable tool for early prediction of response to radiotherapy in gastric cancer.

In a nutshell, it is evident that radiomics hold great promise in facilitating differentiation diagnosis, evaluation of histological degree and tumor stage, as well as response to therapy and prognosis in gastric cancer.

Challenges and Future Prospects

Although radiomics holds the promise to empower the next major breakthrough in precision medicine of gastric cancer, it is still in its infancy. Challenges are facing both radiomics itself and its application in gastric cancer.^[5,6,37]

Each of the four process of radiomics has its unique challenges

Image acquisition

The power of radiomic models is dependent on sufficient patient population. Extracting a large number of imaging features from a small dataset is likely to reduce its power and increase the risk of overfitting. Robert *et al*^[21] recommended that at least ten patients are needed for each feature in binary classifiers. Given the number of radiomic features derived, patient population was relatively small for the majority of the previous publications. In addition, most of the investigations were retrospective analyses based on images from more than one scanner, variable slice thickness as well as multiple reconstruction algorithms. Variations in image acquisition parameters and reconstruction is likely to introduce alteration of the features that are not caused by the underlying biologic mechanisms, resulting in redundant or less reproducible

features.^[38] Mackin *et al*^[39] reported that the bias of features derived from multiple scanners was comparable to those extracted from one scanner. Kim *et al*^[40] identified that compared with inter-reader variability, bias caused by variable reconstruction algorithms weights more. The analysis by Midya *et al*^[41] revealed that image acquisition parameters such as tube current, noise index, and reconstruction technique had strong influence in the reproducibility of radiomics features. Smoother reconstruction algorithms and thinner slices are considered favorable factors for improving the reproducibility of the extracted features.^[42] Given that non-standardized imaging protocols are inevitable at the moment, extensive disclosure of the imaging protocols is recommended to facilitate reproducibility and comparability of radiomics studies.^[6]

Image segmentation

Variable manual and semi-automatic segmentation methods were used to derive ROI- or VOI-based features among the radiomics investigations of gastric cancer. The segmentation determines which voxels within an image are analyzed and serves as one of the most critical steps in the radiomics workflow. The variability in segmentation can introduce bias into the derived features. Computer-aided edge detection followed by manual curation is currently considered the optimum segmentation method for reproducibility. A migration towards deep learning and advanced neural network approaches may be more useful and can compensate for the variability of manual segmentation.^[5] Although two-dimensional ROI-based features are easier to obtain with less labor consumption and faster calculations, it is assumed that these features were unable to accurately reflect the heterogeneity of an entire tumor.^[43] The efficiency of three-dimensional VOI-based features will be compromised due to larger partial volume artifacts along the z-direction.^[42] The work by Li *et al*^[17] reported that VOI based features pales in comparison with ROI based features in predicting of the prognosis of radical resection. The perspectives on whether ROI-based features are superior in reproducibility and implementation compared with VOI-based features requires further studies.^[42,44]

Feature extraction and selection

Various software and programs were utilized for feature extraction in the radiomics studies of gastric cancer. Filograna *et al*^[45] called for the software used for feature extraction to be open-sourced to facilitate external validation and further optimize the constructed models. What's more, not all features extracted will be useful for classifiers. The derived features should be exploited, and those that lack robustness should be eliminated. The performance of the radiomics model can be variable based on different feature selection methods.^[46] Avanzo *et al*^[6] advocated that the process of feature reduction or exclusion needs to be documented clearly.

Model construction and validation

Different techniques are associated with distinct inherent limitations.^[47] The choice of modeling technique has been

shown to affect prediction performance.^[48] Nevertheless, the prediction model is often a single technique selected according to the preference and experience of the performers in almost all existing studies. The key point of model selection is that the work is entirely reproducible.^[42] Although validation is an indispensable component of a complete radiomics analysis, only a sub-set of prior studies was internally or externally validated. Researchers must assess whether the model is predictive for the target patient population or only for sub-sets of the samples analyzed. Ideally, the models should be externally validated.^[19]

Future direction of radiomics in gastric cancer

Further development of radiomics in gastric cancer should be focused on the following three respects. First, although NAC is widely recommended, evidence-based studies of its role in the improvement of long-term prognoses are still absent.^[49] Radiomics has been applied to predict the short-term efficacy of NAC, yet its role in the prediction of long-term survival after NAC has not been investigated and future researches will be warranted. Second, the identification of specific cancer sub-groups, such as cases of HER2 overexpression or programmed cell death-1 ligand 1-positive cases, is of great clinical significance in the selection of candidates for targeted chemotherapy or immunotherapy.^[24,50] Last but not least, nearly all published radiomics studies focused on single modalities, yet hybrid images are likely to hold more information and can develop a more complete picture of the tumor.^[19] Multimodality imaging-based radiomics merits future study.

Conclusions

As a product of cooperation between medicine and engineering, radiomics serves as the frontier of decision making in gastric cancer by using advanced algorithms. While radiomics is still in the early phases, a number of details of its workflow need to be refined, and a large amount of researches are urgently needed to be carried out. It is convinced that with the continuous accumulation of data and standardization of work-flow and improvement of artificial techniques, radiomics will make great breakthroughs in precision medicine of gastric cancer.

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Conflicts of interest

None.

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