· Hot Topics on Radiomics · **· 影像组学专题 ·**

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Preface

Medical imaging is widely used to aid decision-making in clinical practice including oncological management. With the development of technology of medical science, the role of medical imaging as a diagnostic tool is evolving to be a key factor toward personalized precision medicine. Recently, radiomics was proposed to convert medical imaging as minable high-dimensional data, and used to decode the information related to tumor pathophysiology. The process used in radiomics includes the extraction and identification of high-dimensional quantitative radiomics features, subsequent data mining and clinical application. With radiomics, innumerable quantitative features can now be extracted from medical images such as CT, MR, and PET, and used for construction of the clinical-decision support systems.

Many studies have demonstrated that radiomics could be used to improve diagnosis, prognostication, prediction of genotype and treatment response, etc., and to bridge the gap between medical imaging and personalized medicine. In addition, radiomics incorporating clinical information and histopathological and molecular characteristics could deliver more accurate medical care.

In this Special Issue on *Journal of Central South University (Medical Science)*, we organized 10 articles on the advances and applications of radiomics in oncology, including hepatocellular carcinoma, gastrointestinal tumors, prostate cancer, breast cancer, etc. These studies are mainly related to the application of radiomics in prediction of treatment response, characterization, and grading of tumors. We hope these studies could provide the radiologists and oncologists with radiomics approach in adding the oncologic decision-making.

Radiomics and its advances in hepatocellular carcinoma

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ABSTRACT Liver cancer is the second leading cause of cancer-related death worldwide, so early detection and prediction for response to treatment is of great benefit to hepatocellular carcinoma (HCC) patients. Currently, needle biopsy and conventional medical imaging play a significant and basic role in HCC patients' management, while those two approaches are limited in sample error and observer-dependence. Radiomics can make up for this deficiency because it is an emerging non-invasive

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technic that is capable of getting comprehensive information relevant to tumor situation across spatial-temporal limitation. The basic procedure for radiomics includes image acquisition, region of interest segmentation and reconstruction, feature extraction, selection and classification, and model building and performance evaluation. The current advances and potential prospect of radiomics in HCC studies are involved in diagnosis, prediction for response to treatment, prognosis evaluation and radiogenomics.

KEY WORDS radiomics; hepatocellular carcinoma; detection; prediction for response to treatment

影像组学及其在肝癌中的进展

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[摘要] 肝癌(hepatocellular carcinoma，HCC)是全球癌症相关死亡的第二大原因，因此早期发现和治疗反应的预测对HCC患者有很大益处。 目前，穿刺活检和常规医学成像在HCC患者的管理中发挥重要且基础的作用，而这两种方法分别存在样本误差和操作者依赖性的不足。 影像组学是一种新兴的非侵入性技术，可以突破时空限制来获取肿瘤的综合信息，用以反映肿瘤的情况，从而弥补上述方法的不足。影像组学的基本步骤包括图像的获取，感兴趣区的划分与重建，特征的提取、划分与分类，模型的建立与效能评价。影像组学在HCC的诊断、治疗和评价方面取得了一定的进展，具有应用前景。

[关键词] 影像组学；肝癌；检测；治疗反应的预测

As cancer is the second leading cause of death globally, accounting for 8.8 million deaths in 2015, many cancer patients are diagnosed at intermediate and advanced stage, which leaves them no more choice of medical treatment but palliative care. Current clinical practices are counted on conventional medical imaging and needle biopsy. However, needle biopsy cannot provide comprehensive information about tumors with a single sample[1]. Conventional medical imaging can only provide simple traits of tumor to radiologists, such as shape, enhancement and size, due to the limitation of human on gray level with naked eye, while computer assisted interpretation of information in medical images, termed radiomics by Lambin et al[2], can acquire much richer high throughput quantitative features, containing the fields of texture, heterogeneity of lesion, etc.

Spatial-temporal heterogeneity of tumors, as the aggressiveness modulators of tumors and leading reason of treatment failure, cannot be completely evaluated by invasive needle biopsy with a single sample[3]. But this difficulty can be solved with radiomics, because medical images can be acquired routinely throughout the whole course of tumors (from occurrence prediction to prognosis surveillance) and provide comprehensive 3-dimentional information[4]. Thus, radiomics, an ideal image biomarker, can contribute to tumor diagnosis, choice of therapeutic strategy, response prediction, and surveillance of prognosis.

Hepatocellular carcinoma (HCC) is a high incidence and mortality caner in worldwide[5]. However, conventional medical imaging and the HCC related biomarkers contribute little to early diagnosis of HCC, because of the limitation of sensitivity[6-7]. Radiomics is the complementation of this deficiency, which can improve accuracy of diagnosis and contribute to the establishment of individualized treatment.

1 Pipeline of radiomics

The process of radiomics normally concludes 4 steps: 1) image acquisition, 2) region of interest segmentation and reconstruction, 3) feature extraction, selection, and classification, 4) model building and performance evaluation.

1.1 Image acquisition

Image acquisition is the footstone of radiomics that can affect the radiomics result, so the consistency of image acquisition protocol is fundamental to following radiomics procedures, especially for texture feature extraction, which can be affected by scanner manufacturers, image storage formats, and scanning protocol parameters.

1.1.1 Scanner manufacturers

Mackin et al[8] used 17 different CT machines from 4 scanner manufacturers to investigate the influence of scanner manufacturers on texture features and proved that the difference of feature values existed among inter and intra-scanner manufacturers. Even the same phantom images from different scanner manufacturers showed a variation of sensitivity to specific texture features, such as fibrograndular tissue enhancement related features[9].

1.1.2 Image storage format

Apart from scanner manufacturers, image storage formats also can affect radiomics results. Maruyama et al[10] reported that the accuracy of Support Vector Machine and Artificial Neural Network increased from datasets based on JPEG to DICOM format, because DICOM format contains more data capacity and gray level information than JPEG format.

1.1.3 Scanning protocol parameters

The scanning protocol parameters are the most important quality factor for CT and MRI images, such as slice thickness, the echo time (TE), repetition time (TR), etc.[11-12]. Lu et al[13] used concordance correlation coefficients to evaluate inter-setting agreement of quantitative image features among 3 kinds of slice thickness. They found a negative correlation between slice thickness and concordance correlation coefficients. Besides the consistency of data, the performance of model will also be affected by different thickness. He et al[12, 14-15] reported that all non-contrast texture features containing morphological and first order features derived from thinner slice thickness images achieved a better diagnostic performance in both training and validation cohorts. Interestingly, they considered that the poor diagnosis performance of enhancement features was attribute to the contrast material, which may confound the values of radiomics features. However, contrast enhancement features normally can afford additional information of angiogenesis, which is fundamental difference between benign and malignance lesion.

A standard scanning protocol should be promoted and recommended in nationwide and worldwide, accounting for a reduction of the variability in radiomics features and improve the performance of radiomics model [16-17].

1.2 Region of interest segmentation and reconstruction

Regions of interest (ROIs) generally are segmented into two-dimensional images and then reconstructed to a three-dimensional image by software. Manual segmentation, a generally adopted but laborious approach, will cause significant variation of ROI segmentation because of the observer-dependent lesion selection criteria. Automated segmentation can be divided into fully automated segmentation and semi-automated segmentation by artificial participation or not. A new designed software or algorithm to identify specific lesion is the basic characteristic of fully automated segmentation, which means that the accuracy and stability of ROI segmentation depends on this newly designed software or algorithm[18-19]. Apart from the characteristic of time-saving, semi-automated segmentation can acquire more accurate lesion contour and perform more stable lesion definition compared to manual segmentation[20].

1.3 Feature extraction, selection and classification

Feature extraction and quantification is the process of converting images to quantitative data, which can be accomplished by suitable algorithms or software programs, such as 3D-Slicer[21], MITK[22], and so on.

1.3.1 Texture feature category

These texture features mentioned above are generally divided into two types of semantic features and agnostic features. Agnostic features are extracted from images, and can divide to first order features, second order features and higher order features, according to its quantity of voxel.

Semantic features are normally used to describe the lexicons' size, shape, location, vascular distribution and so on. Semantic feature, treated as a relatively subjective feature—even "worrisome" imaging features, still played a good performance in radiomics result, such as in prediction of disease progression, detection of microvascular invasion, prediction of gene expression, and so on[23-25]. Segal et al[25] reported that a specific series of semantic features can predict the gene expression patterns of HCC.

First order features, also named intensity features, rely on individual voxels values and describe its distribution, which means first order features contain no spatial information. First order features are extracted from voxels intensity histogram and also can be used to measure or describe the histogram, such as variance and mean absolute deviation for histogram density, kurtosis for flatness, skewness for asymmetry, entropy for randomness, and so on[26-27].

Second order features and high order features reflect the interrelationship between adjacent voxels. Second order features are normally gained from gray level co-occurrence matrix and gray level run length matrix. The high order features are gained through a progress name 'filtering', which uses complex mathematic models or transforms to extract a series of patterns from image. For example, fractal analysis is an approach to identify specific pattern. And Minkowski functional is an approach which only estimate the intensity of pattern voxel beyond setting threshold value[28]. Wavelet is an approach to extract feature-wave by decomposing computing image. Fourier transform is an approach to extract multiple orientation gradient information from image[29-30].

1.3.2 Feature selection

One high-throughput image can extract abundant features, but utilization of all features to make statistical analysis will inevitably result in over-fitting or false discovery. Suitable dimension reduction and statistical models or systematic mathematic algorithm can choose optimal features to improve the generalization of radiomics model, such as Fisher score, Chi-squared test, Wilcoxon, sequential forward search algorithm, sequential backward search algorithm and others[12].

Generally, feature selection includes two types—classifier-dependent and classifier-independent approach. The classifier-dependent approach contains Wrapper and Embedded, while classifier-independent approach is Filter. The fastest and most commonly used approach is Filter, which is more efficient in features selection[31]. Filter contains a mass of detail approaches, such as Fisher score, *t*-test score, Chi-square score, Wilcoxon, and so on. Parmar et al[32]examined the precision and stability of 14 types of feature selection approach, and the above 4 types of filter showed relatively remarkable performance.

1.3.3 Feature classification

An accuracy test, such as receiver operating characteristic (ROC) curve and area under curve (AUC) is generally adopted in simple binary outcome. But more practical situation is to build a radiomics model to classify the agnostic data. The most common classifier is to use machine learning model, such as decision trees, neural network, support vector machine (SVM), random forest (RF), generalized linear models, and so on. These several machine learning models are just a small part of machine learning approaches. RF has become a popular machine learning model because it can combine radiomics with clinical variables perfectly into an integrated model as well as preserve predictive performance of radiomics and clinical variables. In evaluation of different categories of prognostic factors, RF can show a good performance[33-34].

SVM, another common model in computer-aided detection or diagnosis field, can divide data point to two classes by adding a restriction, such as with or without responder, malignance or benign[35-37]. So the SVM is usually utilized in prediction or evaluation of clinical data through texture features. Neural network as classical machine learning methods contains many different subset model, such as back propagation neural network, radial basis function neural network, convolutional neural network (CNN), and so on. CNN is a feed-forward neural network, which can operate directly on raw radiology images, whereas other model need prior texture feature extraction. CNN as a deep learning method has manifested greater performance in feature classification, accounting for its learning complex feature ability with hierarchy approach. Therefore, CNN is used not only in feature selection and classification, but also in automated ROI segmentation[38-39].

1.4 Model building and performance evaluation

Once machine learning model finish features selection and classification, the radiomics model is completed. For the purpose of model performance evaluation, there will set a patient group for validation. So the process of model building also name training process (training machine learning model). Validation can evaluate the generalization of machine learning model. The most common approach among cross validation is leave one out cross-validation (LOOCV), which use all data to train model except one data for validation[40-41]. When comparing different models' performance, the net reclassification improvement can provide more information about models' performance than ROC/AUC [12, 42].

2 Radiomics in HCC

Liver cancer is the fourth leading cause of cancer-related death worldwide, and have caused 788 thousand people died per year according to WHO[43]. For HCC patients, early detection and diagnosis, prediction of treatment response, and prognosis evaluation are the most crucial issues.

2.1 Diagnosis

In worldwide, American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL) and Japanese Society of Hepatology (JSH) and Asian Pacific Association for the Study of the Liver (APASL) agree that contrast-enhanced computed tomography (CECT) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) play important role in the diagnosis of HCC, with typical enhancement pattern (wash-in and wash-out)[44-47]. Clinically, small nodule with atypical enhancement pattern is difficult to characterize for physician and radiologist. Radiomics has the potential to facilitate the detection and characterization of small nodule. Virmani et al[48] reported that B-mode ultrasound image texture feature analysis combined with neural network can significantly improve focal liver lesions classification, reaching a high overall classification accuracy (95%). Li et al[49] reported that machine learning model based on SPAIR T2W-MRI images achieved the best performance in discriminating small subset (hepatic hemangioma, hepatic metastasis, and HCC) of the single liver lesion. The model's misclassification rates were 11.7% (hepatic hemangioma versus hepatic metastasis), 9.6% (hepatic metastasis versus HCC), and 9.7% (HCC versus hepatic hemangioma), respectively. These two machine learning researches show a future of machine learning model in radiomics study. The classification ability of machine learning model including supervised and unsupervised types can facilitate radiomics studies and development.

2.2 Prediction for response to treatment

Currently, choice of therapeutic strategy for HCC patients is dependent on their Barcelona clinic liver cancer advanced stage. But the heterogeneity exists among the same stage HCC patients. Personalized management is needed for each individual patient[50]. Conventional medical images can just partially reflect the post-treatment response, while HCC patients can benefit more from prediction for response to pre-treatment with radiomics. Mulé et al[51] recruited 92 advanced HCC patients treated with sorafenib, and chose optimal features in arterial and portal venous phase to evaluate their survival. They reported that portal venous phase-derived entropy and coarse texture were independent predictors of overall survival in advanced HCC patients with sorafenib, which have been confirmed in validation group. Akai et al[52] reported that dynamic enhancement CT texture analysis was helpful in predicting the prognosis of hepatectomy. This study included 127 patients and extracts 96 features to train random survival forest model. The concordance index with random survival forest was (61.1±6.0)% for disease free survival, and (70.1±5.5)% for overall survival. Both studies have evaluated the predictability of clinical data and reported none of their clinical data associated with the prediction for response to treatment. On the contrary, radiomics can provide more precise and richer information to predict the pre-treatment response.

2.3 Prognosis evaluation

Microvascular invasion (MVI) is a common independent predictor of HCC patients' prognosis, because it is not only highly correlated to early recurrence but also effects treatment selection (hepatectomy or orthotopic liver transplantation)[53]. But the diagnosis of MVI is not reliable in needle biopsy and the conventional radiology image. Bakr et al[54] built a machine learning model—sparse linear regression with 28 patients' contrast enhancement CT image to predict the occurrence of MVI. Their validation has shown a relative robust machine learning model to identify MVI (AUC 0.76±0.18). Radiomics based on MRI with new technic—diffusion kurtosis imaging is also a potential non-invasive predictor of MVI[55]. And radiomics model combining texture features and clinical data, such as AFP and hepatitis status, can show more accurate preoperative identification of MVI[56-57]. Interestingly, in Bakr's study, clinical data have no significant statistical relationship with MVI and are unable to predict the MVI occurrence, such as AFP and hepatitis status[55]. But Zheng et al[56] reported that radiomics model combine texture features with AFP and hepatitis status exhibited a good performance in MVI prediction. Thus the prediction performance of clinical data needs further investigation. There is no doubt that radiomics can be an independent predictor of MVI.

Apart from MVI, texture feature can also indicate HCC patients' prognosis. Park et al[58] recruited 96 HCC patients treated with transcatheter arterial chemoembolization (TACE), and reported that CT texture features in atrial phase are highly correlated to HCC patients' complete response after TACE, such as higher subjective tumor attenuation, gray-level co-occurrence matrix, and so on. Zhou et al[59] recruited 431 HCC patients underwent partial hepatectomy and extracted 300 features from CT images. Twenty-one selected features by the least absolute shrinkage and selection operator (LASSO) model used to build radiomics signature. The AUC of the radiomics signature (0.817) is higher than that of the clinical model (0.781). And the combined model showed the best result, with an AUC of 0.836. Although these studies have reported that their texture features could predict patients' prognosis, the specific relationship between texture features and MVI/prognosis has not yet been clarified and which needs further study.

2.4 Radiogenomics

Radiogenomics is an exposition of correlation between imaging features with gene expression patterns, gene mutations, and other genome-related characteristics. Theoretically radiomics can extract information from lesion, so image features can reflect intrinsic tumor heterogeneity or gene phenotype. There are limited radiogenomics research in HCC. This could be a hot area in the future. In recent study, Segal et al[25] evaluated the correlation between radiomics features and HCC gene phenotypes, and reported that 78% of the HCC gene expression profiles can be reconstructed by this feature combination, but the specific relation is still not identified. In this study, some semantic features were subjective, such as the percentage of necrosis, which would inevitably influence analysis result. Interestingly, they reported that atypical enhancement model (wash in without wash out) is associated with Hoshida-S2 signature, but the feature enhancement ratio is not significantly associated with HCC gene signature, which may need more patients to investigate. Banerjee et al[60] reported that their computed tomography radiogenomic biomarker can predict MVI and the overall survival of patients. Besides Taouli et al[61] reported that infiltrative type features are highly related to HCC vascular invasion gene expression, which means that MVI may been predicted.

3 Conclusion

To date, radiomics has shown promise for diagnosis, choice of therapeutic strategy, response prediction, and evaluation of surveillance and prognosis. And radiomics is bridging the gap between personalized management and computer-aided prognostics. As more novel treatment methods [image guided radiotherapy (IGRT), breathing adapted radio therapy (bART), immunotherapy] are available today, radiomics will pave the way for performance of individualized therapeutic strategy. Except these innovative treatment, radiomics is one of the most promising implements to transform latest research outcome from bench to bedside, such as prediction of HCC epigenetics and HCC or intrahepatic cholangiocarcinoma (ICC) occurrence caused by different necroptosis microenvironment[62]. With the emergence of big data facilitating the combination and development of radiomics and machine learning approach, we are facing a new era—artificial intelligence (AI)-based quantitative imaging technologies, where the radiomics is an ideal clinical biomarker for hepatocellular carcinoma.

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