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MINIREVIEWS

Application of radiomics in hepatocellular carcinoma: A review

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Abstract

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer with low 5-year survival rate. The high molecular heterogeneity in HCC poses huge challenges for clinical practice or trial design and has become a major barrier to improving the management of HCC. However, current clinical practice based on single bioptic or archived tumor tissue has been deficient in identifying useful biomarkers. The concept of radiomics was first proposed in 2012 and is different from the traditional imaging analysis based on the qualitative or semi-quantitative analysis by radiologists. Radiomics refers to high-throughput extraction of large amounts number of high-dimensional quantitative features from medical images through machine learning or deep learning algorithms. Using the radiomics method could quantify tumoral phenotypes and heterogeneity, which may provide benefits in clinical decision-making at a lower cost. Here, we review the workflow and application of radiomics in HCC.

Key Words: Hepatocellular carcinoma; Radiomics; Machine learning; Deep learning; Radiogenomics

Core Tip: The high molecular heterogeneity in hepatocellular carcinoma poses huge challenges for clinical practice or trial design and has become a major barrier to improving the management of hepatocellular carcinoma. Radiomics could quantify tumoral phenotypes and heterogeneity, which may provide benefits in clinical decision-making at a lower cost. Here, we review the workflow and application of radiomics in hepatocellular carcinoma.

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INTRODUCTION

Liver cancer is one of the most common malignant tumors worldwide. There are approximately 906000 new cases and 830000 deaths every year, ranking as the sixth most commonly diagnosed cancer and the third mortality[1]. Hepatocellular carcinoma (HCC) comprises 75%-85% of cases of primary liver cancer. There is high molecular heterogeneity in HCC at three levels, including the heterogeneity between tumor nodules within the same individual (intertumoral heterogeneity), between different regions of the same tumor nodule (intratumor heterogeneity), and between patients (interpatient heterogeneity)[2]. HCC has one of the fewest somatic mutations in solid tumors that can be targeted by molecular therapies and of which treatment response could not be predicted by mutations in clinical practice[3]. These characteristics of HCC pose huge challenges for clinical practice or trial design and have become a major barrier to improving the management of HCC[4,5]. However, current clinical practice based on single bioptic or archived tumor tissue has been deficient in identifying useful biomarkers[5].

Radiomics was first proposed in 2012 and is different from the traditional imaging analysis based on the qualitative or semi-quantitative analysis by radiologists[6]. This method refers to high-throughput extraction of large amounts of high-dimensional quantitative features from medical images through machine learning (ML) or deep learning (DL) algorithms[7,8]. These features that have been transformed into minable data could be used for diagnosis, treatment evaluation, and prognosis prediction[9]. Using the radiomics method could quantify tumoral phenotypes and heterogeneity, which may provide benefits in clinical decision-making at a lower cost[10,11]. Here, we review the workflow and application of radiomics in HCC.

WORKFLOW OF RADIOMICS

The workflow of radiomics mainly includes: image data acquisition and preprocessing, the volume of interest (VOI) segmentation, feature extraction, model establishment, and performance validation (Figure 1)[9].

Data acquisition

Although radiomics was first and widely utilized in computed tomography (CT) and magnetic resonance imaging (MRI) images, there were more and more studies using ultrasound (US) as well as positron emission tomography images. Most studies were conducted based on retrospective image data sets, even different hospitals and different scanning equipment. The standardized imaging protocols could reduce the unnecessary confounding variability, or it will affect the quality and stability of the extracted imaging features. A previous study found that the feature variability caused by different CT scanners was even comparable to the feature variability found in the tumor[12]. The disclosed imaging protocols were suggested to increase the reproducibility and comparability in future radiomics studies[9].

Segmentation

The three-dimensional VOI segmentation that captures the tumor comprehensive panorama could be delineated by using manual, semi-automatic, and automatic segmentation methods. However, the variability in the segmentation process inevitably introduces bias. Meanwhile, the partial volume effect makes the segmentation challenge that could lead to the blurring of the edge and morphological variation of the lesion. Multiple segmentation is an effective method that can limit bias and help to select robust features, including the evaluation by multiple clinicians and the combination of different segmentation algorithms. However, the commonly used segmentation method in radiomics is manual segmentation and relies on an experienced clinician, which is quite boring and time-consuming. Several semi-automatic or automatic segmentation methods have been reported[13,14]. These

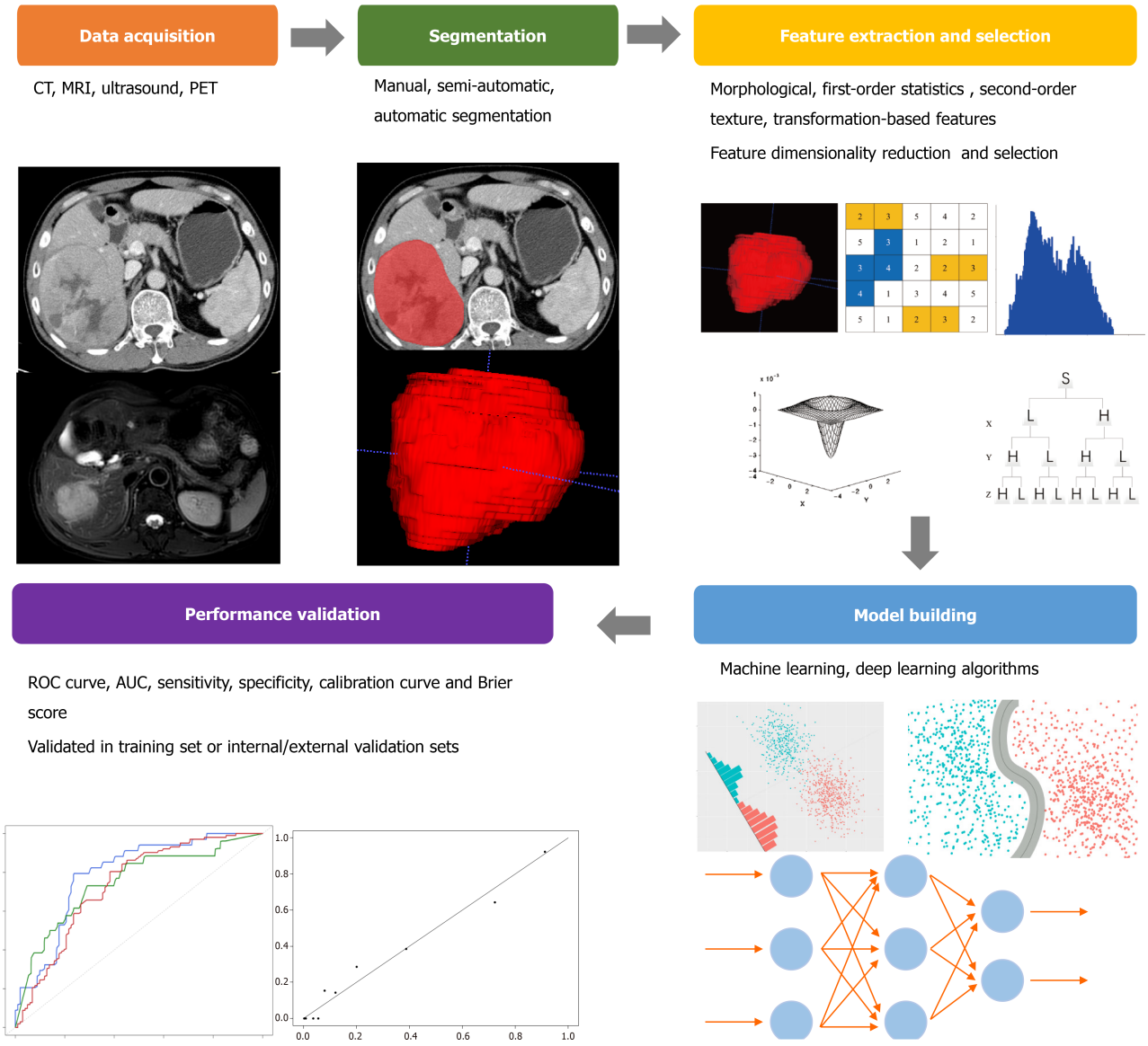

Figure 1 The workflow of radiomics. AUC: Area under the curve; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; ROC: Operating curve.

methods could minimize labor costs and improve the repeatability and reliability of studies but are not widely recognized and applied.

Feature extraction and selection

The high-throughput extraction of quantitative features from VOI is the key process in radiomics analysis after appropriate image preprocessing. The imaging features that are empirically defined by radiologists are named semantic features. These features cannot be described by specific mathematical expressions nor can they be specifically extracted from images, but they are still meaningful in imaging interpretation and clinical application. These non-semantic features quantitatively described by mathematical expressions can usually be divided into four categories: morphological features, first-order statistics features, second-order texture features, and transformation-based features. Morphological features describe the three-dimensional and two- dimensional size and shape of VOI, such as diameter, perimeter, sphericity, and flatness. First-order statistics features (also called histogram features) evaluate the gray-level frequency distribution in VOI, including maximum, median, minimum, and entropy, while second-order texture features are often derived from the gray-level matrix and describe the statistical relationship between voxel gray levels, including gray-level co-occurrence matrix and gray level run length matrix. The voxel gray-level patterns in different spatial frequencies are analyzed by transformation-based features, including Fourier, Gabor, and wavelet features.

According to the number of filters, feature categories, and other parameters, the number of features extracted from the images can be infinite. The inclusion of all relevant features in a predictive model inevitably leads to overfitting, which negatively impacts the efficacy of its prediction performance. It is necessary to introduce a feature selection method to eliminate unsuitable features, that is, feature dimensionality reduction methods (such as principal component analysis or clustering). By reducing redundant and interference items by dimensionality reduction, the features for further analysis contain useful and repeatable information to a large extent.

Model building and performance validation

The prediction model composed of selected features was constructed by an ML algorithm, including support vector machine, random forest, linear discriminant analysis, and so on. The specific method was chosen according to the preference and experience of the researchers. However, different modeling methods have been proved to affect the prediction performance of imaging models and have inherent limitations, such as the independence assumption in logistic regression, feature discretization in Bayesian networks, or network structure dependence in DL. Therefore, a variety of ways could be considered to build the model in the study.

The predictive performance evaluation of the model requires an internal or external validation set to determine whether the model has good generalization performance or only predictability for the specific samples analyzed. This process is often measured by the receiver operating characteristic curve with area under the curve (AUC), sensitivity, and specificity. In addition, the consistency between the observed results and the model prediction was also evaluated necessarily, which can be evaluated by the calibration curve and Brier score. An effective model shows consistency in both training and validation sets. The models validated by an independent external set are more reliable than those validated by an internal set, and of course, the models that could be prospectively verified are more persuasive.

THE APPLICATION OF RADIOMICS IN HCC

Diagnosis

Imaging is a crucial part of the HCC diagnosis. Multiphasic contrast-enhanced CT or contrast-enhanced MRI should be used first with high sensitivity recommended by the European Association for the Study of the Liver[15]. Li *et al*[16] extracted the texture features from the SPAIR T2WI sequence in MRI and used four different classifiers to identify single intrahepatic lesions (hepatic hemangioma, hepatic metastases, and HCC). The error rates were 11.7% (hepatic hemangioma *vs* hepatic metastases), 9.6% (hepatic metastases *vs* HCC), and 9.7% (hepatic hemangioma *vs* HCC). The combination of quantitative apparent diffusion coefficient histogram parameters and the Liver Imaging Reporting And Data System could distinguish HCC from other subtypes of primary liver cancer, such as intrahepatic cholangiocarcinoma and mixed HCC-intrahepatic cholangiocarcinoma[17]. A total of 63 patients confirmed by pathology were included, and it was found that the model combined with gender, Liver Imaging Reporting And Data System, and the fifth percentile apparent diffusion coefficient could achieve a good prediction efficiency. The AUCs could reach 0.90/0.89 with the accuracy of 81.5%/80.0%, the sensitivity of 79.3%/86.2%, and the specificity of 88.9%/77.8% for two independent observers. Huang *et al*[18] managed to distinguish dual phenotypic HCC by different classifiers based on Gd-EOB-DTPA-enhanced MRI and showed good predictive performance.

For the new HCC nodules in patients with a liver cirrhosis background, radiomics features extracted from multiphasic contrast-enhanced CT combined with the ML algorithm could bring benefits. Mokrane *et al*[19] retrospectively included 178 patients from 27 centers and divided them into a training set (142 patients) and validation set (36 patients). All the patients had nodules that were classified as indeterminate liver nodules by the European Association for the Study of the Liver guidelines, and the histological classification was finally confirmed by liver biopsy. A total of 13920 quantitative radiomics features were extracted from the plain, arterial, venous, and dual-phase (delta) phases. Three supervised ML classification algorithms: K nearest neighbor, support vector machine, and random forest algorithm were used to establish the models. A single feature was finally obtained, which represented the characteristics of changes in nodule phenotype between arterial and portal venous phases (corresponds to the "washout" pattern during the contrast agent clearance). Finally,

the radiomics signature used reached an AUC value of 0.66 with a sensitivity of 0.70 and specificity of 0.59 in the external validation set.

US is one of the important methods in the diagnostic algorithm and recall policy by the European Association for the Study of the Liver guidelines[15]. However, US images are more heterogeneous because of the images acquired by different clinicians with multiple examination parameters. There was a study that reported that the features extracted from US images could be classified by using neural network classifiers to distinguish focal liver lesions, including typical and atypical cysts, hepatic hemangiomas, liver metastases, and HCC lesions, with an accuracy of up to 95%[20]. A multitask DL algorithm was constructed that detects and characterizes focal liver lesions in a public dataset[21]. The model simultaneously yielded AUCs of 0.935 for lesion detection and 0.916 for focal liver lesions characterization (benign *vs* malignant).

Radiomics could effectively diagnose and distinguish the HCC lesion from the different intrahepatic lesions, new nodules, and even the subtypes of primary liver cancer. Although the above studies are based on different imaging modalities and ML/DL methods, this method is expected to further assist doctors in clinical diagnosis and decision-making in the future.

Treatment evaluation

Surgical resection is the first choice for HCC patients with good performance status and liver function reserve. But the postoperative 5-year recurrence rate could be as high as 70%. To solve this problem, a multicenter retrospective study was carried out from three independent centers. The study included 295 early-stage HCC patients within Milan criteria who have received preoperative contrast-enhanced CT examination. Recurrence-free survival was selected as the primary endpoint of this study. Based on 177 patients from one center (training set), two prediction models have been constructed that incorporated preoperative variables or postoperative variables. The results showed that the prediction efficiency of the two radiomics-based models was higher than that of previous clinical models and staging systems and can well stratify patients with a low, moderate, and high risk of recurrence.

The application of radiomics in predicting postoperative recurrence has also been verified in other studies. In addition, some studies have found that the radiomics model based on preoperative MRI images can better predict the 5-year survival of patients after hepatectomy. Cai *et al*[22] retrospectively included 112 patients who underwent hepatectomy to predict postoperative liver failure by a radiomics-based nomogram. The AUC value of the training set was 0.822 (95% confidence interval: 0.753-0.917), and the AUC value of the validation set was 0.762 (95% confidence interval: 0.576-0.948). When it was compared with MELD, Child-Pugh, and ALBI score, the radiomics model showed a significant advantage. The researchers conducted a prospective validation analysis of 13 patients who underwent hepatectomy with an AUC of 0.833 (95% confidence interval: 0.591-1.000). Decision curve analysis showed that the model could bring clinical benefits. Radiomic features could identify the tumor invasion and predict recurrence after liver transplantation[23].

Ablation is recommended for HCC patients with Barcelona Clinic Liver Cancer 0 or A stage who are not suitable for surgery. Radiomic features extracted from perioperative CT images could predict early recurrence after curative ablation[24,25]. Among them, the features based on portal vein phase CT images performed best in the validation set. When the clinicopathological factors were added to the model, the portal vein phase-based combined model showed good prediction performance in the training/validation set and significantly better than that of the simple clinical model. Microwave ablation was performed in pigs under CT guidance for improving the visualization of post ablational coagulation necrosis in a proof of concept study[26]. The results showed that radiomic profiles of the fully necrotic areas seemed to be different from those areas with vital tissue. The subregion radiomics analysis could identify these differences with classification algorithms.

Transarterial chemoembolization (TACE) is the most widely used treatment for unresectable HCC in clinical practice. Radiomics plays a role in the prediction of treatment response to TACE[27-29]. Chen *et al*[27] analyzed the radiomic features extracted from tumoral VOI and peritumoral VOI, drawn at the hepatic arterial and non-contrast phases, respectively. The radiomic signature extracted from the peritumoral VOI with expanded 10 mm rim away from the main tumor part achieved excellent performance in predicting the first TACE response. Several studies established a radiomic model based on the preoperative images to predict long-term outcomes of patients who underwent TACE with good performance[30,31]. However, there were various confounding factors during multiple TACE sessions that may weaken the actual predictive performance. Fu *et al*[32] included 520 patients from five

independent centers (divided into a training set and validation set). A comprehensive model including treatment (liver resection or TACE), age, sex, modified Barcelona Clinic Liver Cancer stage, fusion focus, tumor capsule, and three radiomic features was established with good differentiation and calibration. The AUC value of the predicted 3-year recurrence-free survival was 0.80 in the training set and 0.75 in the test set.

Sorafenib is the first oral multikinase inhibitor recommended in patients with advanced HCC. Various clinical trials tried to explore the possibility of combining sorafenib and TACE that may inhibit revascularization and tumor proliferation after TACE. Most of these trials failed, except the TACTICS trial conducted recently. It is important to identify HCC patients who may benefit from the combination of TACE plus sorafenib. A DL-based radiomic model provided a significant prediction value with an AUC value of 0.717 in the training set and 0.714 in the validation set[33].

Radiopathologic evaluation

Microvascular invasion (MVI) of HCC mainly refers to the presence of cancer cells in the endothelial-lined vascular lumen under the microscope, which is a powerful validated, important independent risk factor for early recurrence and poor survival after surgical resection of HCC. Radiomic features extracted from preoperative enhanced MRI multi-phase images could predict the occurrence of MVI favorably[34, 35]. By using the least absolute shrinkage and selection operator method to select appropriate radiomic features, the predictive performance of the combined model incorporating clinicoradiological predictors and radiomic features was better than the clinicoradiological model (AUC 0.943 *vs* 0.850 in the training set, and 0.861 *vs* 0.759 in the validation set). The sensitivity, specificity, and accuracy of the combined model were 88.2%/89.5%, 87.5%/81.4%, and 87.7%/83.9% in two sets, respectively. Several studies reported that using contrast-enhanced CT images to develop and validate radiomics nomogram was a clinically useful tool to identify patients[36,37]. However, a retrospective study that included 495 patients with postoperative MVI status confirmed by histology (MVI- group, n = 346, and MVI + group, n = 149)[38] found that radiomics analysis with current CT imaging protocols does not provide significant additional value to the conventional semantic features.

Pathological grading of HCC is one of the factors that influence prognosis. Most patients with high-grade tumors have a higher rate of intrahepatic recurrence than those without low-grade tumors. The radiomics signatures based on MRI T1WI or T2WI images could be helpful for the preoperative prediction of the pathological grade of HCC[39]. The combination of the radiomic signatures and clinical factors achieved the best predictive performance over the other simple model and distinguished between high-grade and low-grade HCC (AUC = 0.800). In addition, cytokeratin 19 status of HCC that is associated with clinical aggressiveness could be identified by a radiomic-based model with satisfactory prediction performance[40]. Ye *et al*[41] managed to use the texture feature analysis on gadoxetic acid-enhanced MRI images preoperatively to predict Ki-67 status of HCC. However, the optimal cut-off value of the Ki-67 level was defined by the researcher, which weakened the generalization of the study.

Radiogenomics

Gene expression patterns of cancer tissues could reflect the underlying cellular pathophysiology and enrich the understanding of cellular pathways and numerous pathological conditions. Imaging traits have the potential to be a surrogate marker of the clinically relevant genomic/molecular signature of HCC[42-45]. One study found that the dynamic imaging traits from CT systematically correlated with the global gene expression programs of HCC[42]. The combination of 28 imaging traits was sufficient to reconstruct the variation of 116 gene expression profiles, revealing cell proliferation, liver synthetic function, and patient prognosis. Moreover, they developed a two-imaging-trait decision tree, including internal arteries and hypodense halos in HCC that is associated with a gene expression signature of venous invasion and could predict histologic venous invasion and survival of patients. Based on that result, a similar team defined a contrast-enhanced CT imaging biomarker for predicting MVI named radiogenomic venous invasion[43]. In a multicenter retrospective study, the radiogenomic venous invasion biomarker was a robust predictor of MVI with a diagnostic accuracy of 89%, sensitivity of 76%, and specificity of 94% and was associated with a poor overall survival that could have broad clinical use. They considered that radiogenomic venous invasion derived from a gene expression signature of venous invasion may reflect a more fundamental phenotype of the tumor.

Qualitative and quantitative MRI radiomic features could serve as the noninvasive biomarker to predict HCC immuno-oncological characteristics and tumor recurrence [46]. One study analyzed the correlation between radiomics, immunoprofiling (CD3, CD68, CD31), and genomic (PD-1 at the protein level, *PD-L1* and *CTLA4* at the mRNA expression level) features with statistical significance[46]. Radiomic features, including tumor size, showed good prediction performance for early HCC recurrence after resection, while immunoprofiling and genomic features did not.

CONCLUSION

Systemic therapy in advanced HCC has developed rapidly in recent years, with the most prominent success of the combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody). However, due to the huge tumor heterogeneity in HCC, several promising trials (such as keynote-240 and checkmate-459) have failed, and the best objective response rates of successful systemic therapies are only around 30%. In addition, there are more and more ongoing trials in the adjuvant or combination therapies setting of HCC that are explored and practiced currently. Personalized treatment and more precise patient stratification may be required under such circumstances. Radiomics technology based on ML/DL algorithms is expected to become a bridge that connects the clinical personalized precision treatment of HCC patients and its tumor phenotype. Further radiomics research with multicenter and prospective validation is still needed for improving its interpretability and reproducibility.

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