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CURRENT STATUS AND PROGRESS OF MRI RADIOMICS IN HEPATOCELLULAR CARCINOMA

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Abstract: Hepatocellular carcinoma (HCC) is a common malignant tumor in the human digestive tract. It has high recurrence, poor prognosis, and difficulty in early detection. Relative to this, magnetic resonance imaging (MRI) has good soft-tissue resolution and multi-parameter imaging advantages, significant for accurate liver cancer diagnosis and prognosis. Meanwhile, radiomics can extract high-dimensional and quantitative features to quantify tumor heterogeneity, exhibiting great potential in differential diagnosis, risk stratification, and prognosis evaluation of liver cancer. This article reviewed the research progress of the MRI omics of HCC.
Keywords: hepatocellular carcinoma, magnetic resonance imaging, radiomics, accurate diagnosis, risk stratification, prognosis prediction

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer death[1,2]. The five-year survival rate of HCC patients is low, only 18%, and the recurrence rate after five years is as high as 60% to 80% [3,4].

Magnetic resonance imaging (MRI), as a non-invasive imaging modality, is commonly used for preoperative diagnosis, postoperative follow-up and efficacy evaluation of HCC. Conventional MRI diagnosis is mainly based on the radiologist's subjective visual assessment, which is a qualitative diagnosis with low sensitivity and specificity, and it cannot accurately describe the heterogeneity and biological dynamics of HCC. In recent years, thanks to advances in computer technology, quantitative analysis of medical images has opened up new opportunities for clinical practice. Imaging histology was presented in this setting in 2012 by Lambin et al[5,6].

Radiomics is a new technical instrument that extracts potential high-dimensional quantitative features from medical images and examines their relationship to clinical and pathophysiological data to develop suitable models for the diagnosis and treatment of disease useful information. With the advantages of multiparametric imaging, MRI can provide a wealth of qualitative and quantitative information, establishing extensive and profound connections with the diagnosis, prognosis, pathology, and molecular phenotype of HCC, and many models with potential applications can be developed. This article reviewed the current status of radiomic MRI studies in HCC.

2. HCC DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

HCC and hepatic hemangioma are two types of liver tumors, malignant and benign, respectively. In both cases, the need for early diagnosis is critical for patient management. On imaging, both types of diagnosis are based on magnifying the appearance of various stages of the tumor. Diagnosis is difficult in some patients with contraindications to contrast media or in whom contrast media cannot be used for other reasons. The study of Wu et al.[7] combined the imaging histological features of various non-enhanced MRI sequences (T2WI, DWI, iso-inversion) to distinguish HCC from hepatic hemangioma. This study included 446 lesions (222 HCC lesions and 224 hepatic hemangioma lesions) in 369 patients. According to this study, the combined model outperformed less experienced radiologists (two-year experience, AUC of 0.72) and matched the performance of professional radiologists (ten-year experience, AUC of 0.908). There was no statistical difference between the AUC of the histology model and that of experienced radiologists.

For the differential diagnosis of hepatic hemangioma and HCC in non-enhanced cases, radiomics can provide useful diagnostic models and new ideas, and has certain reference value. Primary liver cancers include HCC, cholangiocarcinoma (CC) or combined hepatocellular cholangiocarcinoma (cHCC-CC). Among them, the incidence of cHCC-CC is about 5%. The imaging features of cHCC-CC, CC and HCC are similar and difficult to identify [8]. Liu et al [9] studied 85 cases of HCC (24 cases of cHCC-CC, 24 cases of CC, and 38 cases of HCC) using 1.5T, 3.0T MRI and CT images, respectively, and classified them into two categories: cHCC and non-cHCC. This study found that using MRI to diagnose patients with cHCC could improve accuracy and make diagnosis and treatment easier.

In addition, MRI radiomics models can be combined with clinically-standard grading systems to improve accuracy. The Liver Imaging Reporting and Data System (LI-RADS) is a typically used imaging grading system in clinical practice to determine the benign and malignant nature of liver mass with high accuracy. The recent LI-RADS guidelines indicated that for HCC lesions larger than 2 cm, the sensitivity was 89.6%, the specificity was

81.2%, and the overall diagnostic accuracy was 88.0%. However, the sensitivity and specificity of LI-RADS grading for small HCC were low[10]. Zhong et al [11] combined an imaging histology model with LI-RADS grading to identify small HCC from benign nodules in cirrhosis. Compared with LI, the combined model improved the specificity (combined model: 97.7% vs. LI-RADS: 81.8%, p=0.030) and the sensitivity (combined model: 99.1% vs. LI-RADS: 92.9%, p=0.031). A correlation diagnostic model was also developed to evaluate 65 HCC lesions (36 HCC, 17 CC, and 12 cHCC) by combining gender and LI-RADS grading, with an AUC of 0.9 and a sensitivity and specificity of 79.3 % and 88.9%, respectively. Thus, radiomics can diagnose more difficult HCCs by potent combination with clinical grading criteria.

Dual-phenotype HCC (DPHCC) is a subtype of HCC identified in 2015[13]. Some cancer cells in DPHCC express both HCC markers (e.g. Heppar-1, CK18, CEA) and CC markers (e.g. CK7, CK19). DPHCC is more aggressive in malignancy and aggressiveness than HCC[14]. Huang et al [15] used histological features retrieved from gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) enhanced MRI sequences to differentiate the two. The results identified that the histological model based on the portal venous phase performed better prediction, with an AUC of 0.79. The study concluded that imaging histology can noninvasively diagnose dual-phenotype HCC. However, more research is needed.

3. PROGNOSIS PREDICTION OF HCC

HCC prognosis prediction and classification play a vital role in personalizied treatment of HCC patients. However, the reproducibility and reliability of current HCC risk classification approaches are still insufficient, and more research is needed. Wang et al [16] extracted 150 histological features (44 enhanced sequences, 42 DWI sequences, 29 T1WI sequences and 35 T2WI sequences) from T1WI, T2WI, DWI, and enhancement sequences of 201 HCC patients with survival predictive value, and combined them with the patients' alpha-fetoprotein and glutamate transaminase levels. A model was established using random forest techniques to predict the five-year survival rate of HCC. The results showed that the predicted five-year survival rates for the training and validation groups were in good agreement with the actual five-year survival rates. Zhang et al [17] investigated the association between texture features and postoperative survival in MRI images of HCC, cholangiocarcinoma, and mixed HCC. They discovered that texture features were independent predictors of overall survival. The texture features of tumors with different prognosis vary that tumors with poor prognosis (such as CCs) have more variable texture features, while tumors with better prognosis (such as HCC) have more uniform pixel distribution and less diversity of texture features. However, few studies have applied imaging histology to predict overall survival in HCC, and further studies are needed to support this conclusion.

4. PREDICTION OF POSTOPERATIVE RECURRENCE OF HCC

Surgery is currently one of the most effective curative treatments for HCC. However, postoperative recurrence seriously impacts the treatment outcome and survival of HCC patients [28,29]. Thus, predicting recurrence is helpful for risk stratification of HCC patients and provides a reference for their personalized treatment. Relevant MRI models have been used to predict recurrence after hepatectomy. Hui et al [30] extracted texture features from preoperative MRI images of 50 patients (20 with early recurrence and 30 with non-early recurrence) and constructed a model for predicting recurrence 730 days after liver resection. They found that the sum variance S (4, 0) of delayed period images of enhanced MRI was closely associated with postoperative recurrence, and the accuracy of prediction was 0.84. Zhao et al [18] constructed 12 models to predict early recurrence after hepatectomy based on the histological characteristics of different sequences (homophobic T1WI, antiphase T2WI, T2WI, arterial phase, portal phase, delayed phase, and DWI). They determined that a simple histological model combining six sequences (homophobic T1WI, antiphase T2WI, T2WI, arterial phase, portal phase, and delayed phase) had the highest predictive efficacy, with an AUC of 0.5. The best predictive performance was achieved with an AUC of 0.771. Additionally, the overall best predictive performance was achieved with an AUC of 0.87, the sensitivity of 0.8 and the specificity of 0.72, combining histological and clinical models, such as microvascular invasion, pathological grading and tumor diameter. These findings required further evidence.

Nowadays, surgery is usually indicated for patients with early-stage HCC. However, due to the insidious onset of HCC, patients have usually been in the middle to late stage and may lose the opportunity for getting surgical treatment [19]. For intermediate and advanced HCC patients, transcatheter arterial chemoembolization (TACE) provides a safer and more reliable treatment. From a 2008-to-2009 study on the characteristics and treatment of HCC in China, around 61.7% of intermediate and advanced HCC patients were treated by TACE. However, tumor microenvironment hypoxia and tumor cell remnants after TACE would often lead to tumor recurrence, with a rate as high as 50-80% [20,21]. Song et al [22] extracted histological features from the preoperative MRI dynamic enhancement portal phase of TACE, in which the resulting model that integrated clinical and imaging factors had an AUC of 0.80. Compared to previous CT-based histological models constructed by Yuan et al [23] and Zheng et al [24], the efficacy of this model was significantly higher. Predicting recurrence after TACE (AUC of Yuan model: 0.755; AUC of Zheng model: 0.587) may be associated with the better resolution of soft tissues by MRI. However, it is a single-center study that more evidence is needed.

5. MICROVASCULAR INVASION PREDICTION IN HCC

Microvascular invasion (MVI) is a risk factor for HCC recurrence after surgery, and its early detection is essential. It denotes nesting masses of cancer cells seen microscopically in the endothelium-lined vascular lumen, most commonly in the small branches of the portal vein within para-cancerous liver tissue. It was seen in 20% of patients who had received in situ liver transplantation and 50% of those who had undergone hepatectomy [25–28]. Many diagnostic models, primarily CT and MRI, have been developed for predicting MVI in HCC, with their performance outperforming CT models and the advantage of multiparametric imaging in MRI. For instance, Meng et al [29] evaluated the diagnostic model performance of different imaging modalities (CT, MRI) for predicting MVI. The results revealed that the diagnostic model performance of MRI was superior to that of CT (AUC^{MRI}: 0.804 vs. AUC^{CT}: 0.801).

Furthermore, clinical and imaging features like increased methemoglobin expression, tumor margin irregularity, and periarterial enhancement are associated with microvascular invasion. Therefore, combining imaging, clinical and radiomics features can improve model efficacy. As an example, Yang et al [30] integrated these parameters with imaging histology to develop a diagnosis model with an AUC of 0.943 and with sensitivities and specificities of 88.2% and 87.5%, respectively.

Furthermore, merging several sequences to establish a radiomics model is a great idea. Nebbia et al [31] extracted 100 three-dimensional radiomics features from different sequences of T1WI, T2WI, DWI, late arterial, and portal venous phases to construct individual sequence and combined sequence models. The results showed that the combined model (T2 sequence combined with T1 sequence) performed the best. The initial study demonstrated that the accuracy of MRI-based imaging histology models for predicting MVI in HCC was high and had therapeutic relevance. However, various aspects like sample size, reproducibility, and modeling methodologies influenced the applicable models. Thus, their accuracy must be evaluated using larger samples and more rigorous approaches.

6. PATHOLOGICAL GRADE PREDICTION OF HCC

The pathological grade of HCC is a vital factor influencing survival, recurrence, and metastasis. High-grade HCC has a higher risk of recurrence than a low-grade one. Several studies have found a possible association between imaging histology and pathological grading. Zhou et al [32] investigated and compared the arterial phase texture features of MRI Gd-DTPA enhancement in different HCC grades, such as histogram, gray travel length coding, and gray coeval matrix, and discovered that mean intensity values and gray travel matrix values in four directions in the MRI images of HCC could capture the pathological grading features of high and low tumor differentiation. Wu et al [33] developed a model to predict the pathological grade of HCC based on AFP expression levels, T1-weighted and T2-weighted sequences. They demonstrated that the model had an AUC of 0.8 in distinguishing between high-grade and low-grade HCC patients. Geng et al [34] evaluated the magnetic sensitivity-weighted imaging sequences of 53 HCC patients using Spearman correlation coefficients, determining 107 correlations between histological features and histopathology. Their findings revealed that 11 histological features in SWI images, including normalized inverse moment, kurtosis, and grayscale inhomogeneity, were significantly correlated with pathological grading. The two studies demonstrated the utility of imaging histology techniques in tumor grading. Nevertheless, more and larger sample-size studies are required.

7. RADIOGENOMICS

The rapid progress of genomics in the 1990s revolutionized the diagnosis and treatment of HCC. The development of HCC is closely related to genes, for genetic testing plays an essential role in diagnosing and treating HCC [48]. However, genetic testing is invasive, time-consuming, and expensive. Therefore, it cannot be evaluated for all patients [49]. Radiogenomics can uncover the relationship between the imaging histological features of HCC and genes noninvasively and at a relatively low cost. It may play a role in diagnosing and treating HCC instead of genetic testing. Ki-67, GPC-3, and CK-19 are closely associated with HCC prognosis and are now extensively used in clinical practice. In 1983, Gerdes discovered Ki-67 protein, a proliferating cell-associated antigen widely expressed in all cell cycle phases (including G1 phase, S phase, G2 phase, and mitotic phase, except G0 phase) [35]. Many studies have determined that Ki-67 is strongly associated with pathological grade, survival, recurrence-free survival, and disease-free survival of HCC [36]. A meta-analysis [37] revealed that the higher the Ki-67 expression, the shorter the survival, disease-free survival, and recurrence-free survival of patients with HCC, and the worse the prognosis. Therefore, a preoperative diagnosis of Ki-67 expression is vital for HCC patients. Shi et al [38] found that histogram indices extracted from intravoxel incoherent motion (IVIM) parameter maps could predict Ki-67 expression. Ye et al [39] divided Ki-67 expression in 89 HCC patients into high and low expression groups. Thirteen texture features were extracted from MRI-enhanced images, and clinical and imaging features were combined to construct a predictive Ki-67 model. The results indicated that the combined model's consistency index (C-index) was 0.936. Qin Lili et al [38] selected seven texture features based on T2WI sequences of MRI.

The above three studies demonstrated the potential value of imaging histology as a noninvasive method for assessing Ki-67 expression, and the combined clinical and histological models could further improve the model's predictive ability. They initially suggested that MRI imaging histology could be a tool for predicting Ki-67, but further studies are still needed.

Phosphatidylinositol proteoglycan 3 (glypican3, GPC3), a member of the GPC family, is a specifically highly expressed in HCC and is closely associated with HCC prognosis [39]. Several studies have shown that GPC-3 expression correlates with the pathological grade,

recurrence-free survival, and progression-free survival of HCC. The higher the expression of GPC-3, the worse the prognosis of patients [40 - 43]. Geng et al [34] analyzed the association between the radiomics features of 3.0 TMRI and GPC-3. They determined that the normalization of MRI histological features depended on the inhomogeneous performance to reflect positive GPC-3 expression, and the AUC of the constructed diagnostic model was approximately 0.76. The relevant imaging histological models to predict GPC-3 expression in HCC are still used. Indeed, GPC-3 expression in HCC is still relatively few and requires further confirmed by more studies. If these models can be applied in the clinic, they can help stratify the risk of preoperative HCC patients and provide an essential reference for the personalized treatment of patients.

HCC development is closely related to the immune microenvironment and has become a hot research topic. The molecules that regulate the immune microenvironment of HCC are closely related to imaging histological features. Hectors et al [44] examined the relationship between 282 histological features of multi-phase dynamically enhanced MRI and ADC maps and PD-L1 and CTLA-4 of HCC. They discovered that texture features of MRI-enhanced late arterial phase were significantly associated with PD-L1 and CTLA-4. However, the sample size included in their study is small, and more research is vital for further confirmation.

Immunotherapy plays a vital role in treating HCC by modulating immune checkpoints. However, it has a low response rate of around 20%. Immunotherapy response rate is related to tumor-infiltrating T lymphocytes. Such infiltration can be measured using an immune score tool. Chen et al [45] developed three immunocore models based on intratumoral, peritumoral-intratumoral, and clinical-imaging histology. The combined clinical-imaging radiomics model had a higher diagnostic efficacy (AUC: 0.926) than the other two models (AUC of intratumoral: 0.823, AUC of peritumoral-intratumoral: 0.904). The said study aids in stratifying immunotherapy patients with HCC and identifying immunotherapy-sensitive patients.

8. MRI RADIOMICS BASED ON DEEP LEARNING

As deep learning is making a splash in various image processing fields, the combination of imaging histology and deep learning has further enhanced the performance of imaging histology models. There are two ways to combine deep learning with radiomics. For one way, automatic tumor ROI segmentation is crucial in building an radiomics model. However, traditional manual segmentation by multiple physicians is time-consuming and easily influenced by the reviewer's subjective factors, resulting in long model building times [46]. In addition, the variability amongst different viewers leads to unstable extracted features, which is not conducive to model construction. In this case, deep learning technology can achieve automatic segmentation of tumor target regions, thus shortening the construction time of the imaging histology model and improving the stability and reliability of features [47].

Another way is feature extraction, which uses features extracted by deep learning networks to construct models, improving the generalization ability and accuracy of models. Song et al [48] used deep learning networks to extract the features and combine clinical variables to construct predictive HCC MVI models. The results indicated that the prediction accuracy was relatively high (AUC:0.931 vs. AUC:0.731 for the traditional histology model) compared to the predictive MVI model previously constructed using conventional histology methods. However, deep learning relies on large sample size, and the cost of acquiring extensive sample data in clinical settings is high and challenging to perform in practice. There are still few relatively deep learning of MRI imaging histology models about HCC, which is an area worth exploring.

9. PROBLEMS AND CHALLENGES

Although MRI histology research in HCC has yielded some promising results, there are still numerous issues in clinical practice. For instance, imaging parameters and machines significantly influence MRI radiomics features. Unfortunately, there are still inadequate effective methods to correct the influence of imaging parameters including field strength, b-value, and machine manufacturers on histological models. Consequently, the current studies mostly apply MRI sequences with the same field strength, the same manufacturer, and minor differences in imaging parameters for modeling, resulting in limitations in sample size and model generalization. Furthermore, since the clinical application of high field strength and high precision MRI imaging devices is delayed, developing a histological model based on high field strength, such as 3.0 T MRI sequences, tends to face to challenges like small sample size and short follow-up time in practical operation.

Furthermore, the extraction and screening of features and the selection of modeling algorithms continue lacking of uniform standards, resulting in inconsistent quality across studies and affecting the reliability of imaging histology. Most studies are single-centered, and various histological models still require additional data support.

10. CONCLUSION

Radiomics theory and technology are already well established, and their combination with MRI has proved future uses in the diagnosis, molecular phenotypic prediction, and prognosis assessment of HCC. Compared to CT, MRI provides more excellent soft tissue resolution, the advantage of multi-parameter and multi-sequence imaging, and a more considerable amount of information, allowing the construction of more histological models and the selection of the model with the greatest predictive performance. MRI histology enables MRI to evolve from qualitative to precise diagnosis and treatment. Meanwhile, future development trends are deep learning and artificial intelligence in radiomics to help customize patient treatment.

In the future, researchers will standardize radiomics procedures and validate them using large samples and

multicenter studies. Furthermore, it is frequently challenging in practice to standardize the imaging characteristics of MRI, and how to construct therapeutically appropriate histology models with varying imaging parameters and machine models is a critical challenge. Radiomics will be developed and employed in MRI to provide diagnostic accuracy and efficacy prediction for HCC patients.

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