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Bridging the Gap Between Imaging and Molecular Characterization: Current Understanding of Radiomics and Radiogenomics in Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the third leading cause of cancer-related deaths. Imaging plays a crucial role in the screening, diagnosis, and monitoring of HCC; however, the potential mechanism regarding phenotypes or molecular subtyping remains underexplored. Radiomics significantly expands the selection of features available by extracting quantitative features from imaging data. Radiogenomics bridges the gap between imaging and genetic/transcriptomic information by associating imaging features with critical genes and pathways, thereby providing biological annotations to these features. Despite challenges in interpreting these connections, assessing their universality, and considering the diversity in HCC etiology and genetic information across different populations, radiomics and radiogenomics offer new perspectives for precision treatment in HCC. This article provides an up-to-date summary of the advancements in radiomics and radiogenomics throughout the HCC care continuum, focusing on the clinical applications, advantages, and limitations of current techniques and offering prospects. Future research should aim to overcome these challenges to improve the prognosis of HCC patients and leverage imaging information for patient benefit.

Keywords: hepatocellular carcinoma, radiomics, radiogenomics

Introduction

Hepatocellular carcinoma (HCC) is a leading global cancer and cause of death.[1,2] It often results from viral hepatitis,[3,4] alcohol use, non-alcoholic fatty liver disease (NAFLD), and cirrhosis.[5,6] Early-stage HCC is treated with surgery or transplantation, but most cases are diagnosed late, requiring transcatheter arterial chemoembolization (TACE) and ablation.[7] Combining immune checkpoint inhibitors with anti-angiogenic drugs has improved survival.[8]

Imaging is essential in managing HCC patients, including screening, diagnosis, treatment, and prognosis.[9,10] Ultrasonography facilitates early detection of hepatic lesions. Combined with color Doppler imaging and serum alpha-fetoprotein levels, it aids in characterizing HCC.[11] Dynamic contrast-enhanced CT and multiparametric MRI are useful for diagnosis,[12] while ^{18}F-FDG PET/CT monitors systemic metastasis.[13] Imaging guides non-surgical treatments like local ablation, and TACE requires angiography. RECIST criteria rely on imaging.[14] Despite advancements, HCC survival

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rates remain low, with a high postoperative recurrence rate (70% within five years), primarily early recurrence (within two years).[7] This issue arises from complex molecular mechanisms and HCC's immune microenvironment.[15] Current imaging provides visual data but lacks precise guidance for personalized treatment and prognosis due to limited incorporation of molecular and microenvironmental information.

Research has shown that medical imaging data contains valuable information on tumor heterogeneity, extractable through artificial intelligence (AI) methods.[16] Recent HCC research highlights semantic features in radiomics, bridging quantitative imaging and clinical interpretations. These features, like tumor shape and texture, enhance analysis by providing nuanced insights into tumor heterogeneity.[17,18] As shown in Figure 1, since the advent of Sanger sequencing,[19,20] it has developed over several decades to achieve single-cell resolution. In recent years, spatial transcriptomics has enabled the acquisition of spatial distribution information of different cell types. In 1973, Haralick et al began extracting quantifiable features from medical images.[21] Till 2020, the Image Biomarker Standardization Initiative (IBSI) was released to guide clinical applications.[22] In 2007, the correlation between imaging features and genes was reported for the first time,[23] gradually evolving into the field of radiogenomics, with explores molecular mechanisms and annotates imaging features, aiding in tumor stratification, precision treatment, and prognosis prediction.[24]

Current research in radiogenomics has mainly focused on glioblastoma and lung cancer.[25,26] While imaging is crucial for HCC screening and diagnosis, much remains unexplored regarding phenotypes and molecular subtyping. Despite this, significant advancements have been made in HCC research. This review provides a summary of recent advancements in radiomics and radiogenomics for HCC, discussing clinical applications, benefits, limitations, and future prospects.

Routine Process of Radiomics and Radiogenomics in HCC

The emergence of deep learning has enhanced the utilization of medical imaging data and is currently applied in areas such as medical imaging optimization, radiomics, and radiogenomics (Figure 2).[27] This evolution plays a crucial role in the clinical landscape,[28] where a multimodality medical image underpins the diagnosis and surveillance of HCC, each with unique benefits and collective synergy.[29,30]

In supervised machine learning for medical imaging, labeled clinical data is utilized to train models through predefined formulas, resulting in a trained model capable of classifying or predicting outcomes. Conversely, unsupervised deep learning employs unlabeled data, leveraging convolutional neural networks and algorithms to identify patterns and structures within the data, ultimately forming a model that can discover hidden features without explicit labels (Figure 3). Specifically, in the context of medical imaging, radiomics relies on supervised machine learning techniques, while deep learning based on computer vision embodies the principles of unsupervised learning.[31] Radiomics, grounded in

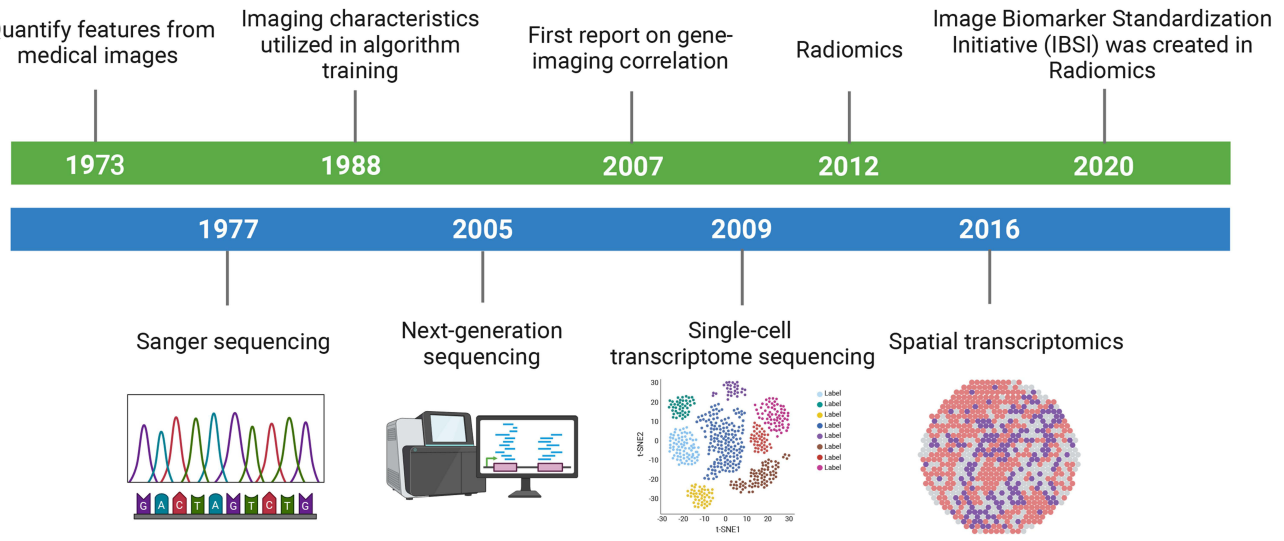

Figure 1 Timeline of advancements in medical imaging and sequencing technologies. Created in BioRender. 7, R. (2024) https://BioRender.com/h50b294.

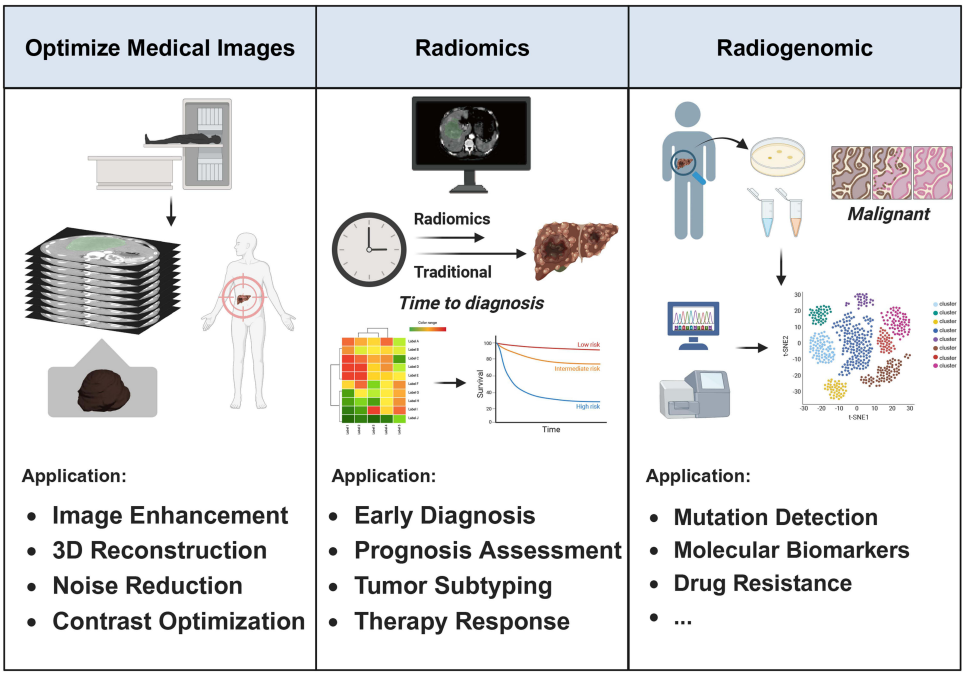

Figure 2 Applications of Medical Image Optimization, Radiomics, and Radiogenomics. Created in BioRender. 7, R. (2024) https://BioRender.com/x47n329.

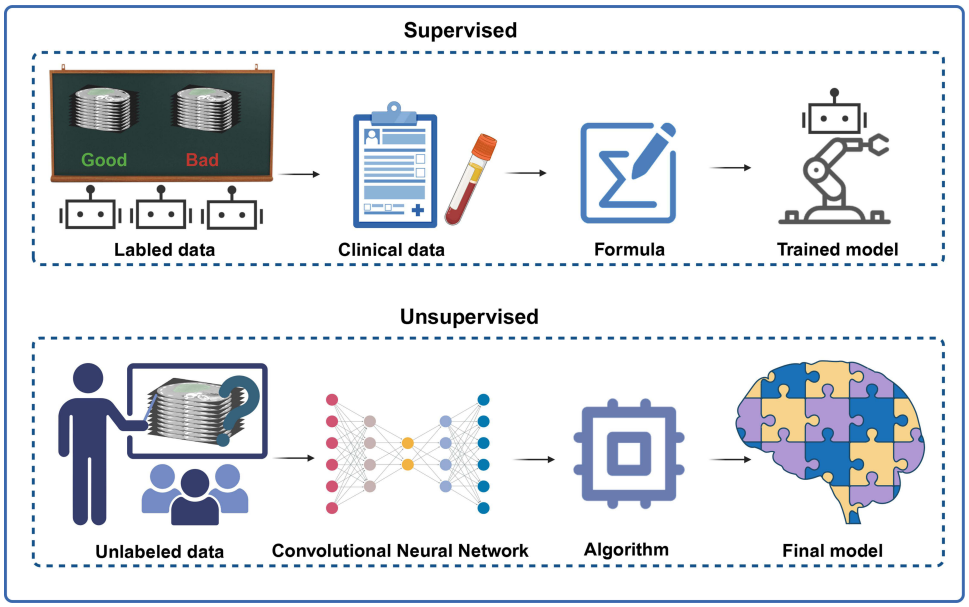

Figure 3 Supervised and Unsupervised Learning in Medical Image Analysis. Created in BioRender. 7, R. (2024) https://BioRender.com/y83w117.

predefined feature extraction, is lauded for its interpretability and clinical relevance. Conversely, deep learning automates this process, unveiling intricate patterns that are not immediately perceptible, albeit with interpretability challenges.[32] However, despite the increasing application of AI in liver cancer imaging, there is still a lack of related clinical trials. It can be observed that most clinical trials use radiomics methods, with the primary endpoints focusing on prognosis, particularly the monitoring of recurrence (Table 1). Therefore, radiomics is mainly discussed in this review.

HCC radiomics workflow, akin to methodologies applied in other oncological contexts like gliomas and lung cancer,[33] begins with the crucial step of imaging data acquisition and the segmentation of regions of interest (ROI).

Table 1 Clinical Trials on Liver Cancer Utilizing Radiomics or Artificial Intelligence

NCT Number	Modality	Methods	Primary Outcome	Interventions
NCT05637788	CT	Radiomics	RFS, OS	Surgery
NCT03981848	MRI	Radiomics	RFS	Liver transplantation
NCT05543304	UNKNOWN	Radiomics	OR	Systemic therapies
NCT03221049	Ultrasound	Radiomics	Liver fibrosis, benign or malignance, recurrence	Diagnosis
NCT05889949	MRI	Radiomics	OS, PFS	TACE+MKIs
NCT02757846	CT	Radiomics	UNKNOWN	Diagnosis
NCT03917017	UNKNOWN	Radiomics, AI	OS	Hepatectomy
NCT03880721	UNKNOWN	Radiomics	RFS, OS	Microwave ablation
NCT05327907	UNKNOWN	Radiomics	HCC/ICC	Diagnosis
NCT04843176	CT	AI, LI-RADS	HCC	Diagnosis
NCT05637788	CT	Radiomics, AI	RFS, OS	Surgery
NCT06334965	PET-MRI	AI	PFS	TARE
NCT04299919	MRI	AI	RFS	Hepatectomy, minimally invasive treatment
NCT05200195	UNKNOWN	AI	RFS	Liver transplantation
NCT04965259	MRI	AI	HCC	Diagnosis
NCT05627297	CEUS, DE-MRI	Radiomics, AI	OS	Hepatectomy, radiofrequency ablation

Abbreviations: NCT, National Clinical Trial; MRI, Magnetic Resonance Imaging; OS, Overall Survival; RFS, Recurrence-Free Survival; OR, Objective Response; AI, Artificial Intelligence; LI-RADS, Liver Imaging Reporting and Data System; HCC, Hepatocellular Carcinoma; TACE, Transarterial Chemoembolization; MKI, Multi-Kinase Inhibitor; TARE, Transarterial radioembolization; CEUS, Contrast-Enhanced Ultrasound; DE-MRI, Dual-Energy Magnetic Resonance Imaging.

This pivotal task is typically undertaken by expert radiologists specialized in abdominal or comprehensive body imaging, ensuring precision through collaborative consensus in complex cases. It can be broadly divided into four steps:

(1) Following the acquisition of imaging data, the regions of interest (ROI) are first segmented. This step is typically carried out by two or more experienced radiologists specializing in abdominal or full-body imaging. In cases of disagreement, additional radiologists may be consulted.

(2) Subsequently, features are extracted from the ROIs. Presently, a method based on PyRadiomics[17] is widely employed, wherein a variety of filters are utilized to extract a corresponding number of features, including histogram and texture features.

(3) Given the large number of extracted features, dimensionality reduction is typically performed based on different outcomes or events to select the most relevant features.

(4) The radiomics features obtained from dimensionality reduction are usually fitted into a linear model to generate a radiomics score (signature). The radiomics score is then optimized by combining clinical indicators or other biomarkers, leading to improved outcome prediction.

Studies in HCC predominantly focus on predicting the prognosis, treatment outcomes, and risk factors of HCC patients.[34] Furthermore, research also delves into utilizing radiomics models to build classifiers to distinguish HCC from cholangiocarcinoma,[35] or to predict high-frequency driver mutations and immune molecular subtypes in HCC.[36–38]

Radiogenomics combines genomics or transcriptomics with radiomics and aims to elucidate radiomics scores and phenotypes at the genetic level.[39] Its primary role lies in interpreting relatively unknown radiomics features using known functional molecules or pathways. Serving as a bridge between visible images and their potential molecular mechanisms, radiogenomics enables early prediction of tumor or microenvironment heterogeneity in patients, facilitating more precise treatment interventions.[40–42] Processing of imaging data follows a similar protocol as outlined earlier, with the integration of whole exon sequencing or RNA-seq data for analysis. Presently, two main methods are employed to explore the relationship between imaging and genes:

(1) Pearson correlation analysis, which investigates the relationship between features or scores and genes of interest. Subsequently, function enrichment analysis is conducted on significantly correlated genes to identify image features reflecting specific biological functions. However, genes obtained through this method typically participate in diverse functions, making it challenging to determine critical genes solely based on correlation coefficients and *p*-values.

(2) Weighted correlation network analysis (WGCNA) categorizes gene sets into distinct functional gene modules.[43] It then identifies gene modules most relevant to radiomics phenotypes or clinically relevant character. For the most relevant gene modules, Module Membership (MM) and Gene Significance (GS) values are computed, and genes representing module functionality, termed Hub genes, are selected based on MM and GS thresholds.[44] Additionally, gene and module relationships are evaluated through the calculation of module eigengene-based connectivity (KME) values, with hub genes selected based on $|kME| \geq$ threshold.[45] Regardless of the method used to select critical genes, biological function annotation can be conducted to establish classification or regression models for interpreting imaging features. Thus, imaging feature information and gene/transcriptome information are integrated.

Comparatively, radiomics and deep learning offer distinct advantages in the imaging analysis landscape. Radiomics, with its reliance on predefined feature extraction, excels in its interpretability and direct clinical applicability. In contrast, deep learning approaches automate feature extraction, revealing complex patterns beyond human detection. However, this "black box" nature poses challenges in clinical interpretation and validation.[46]

In summary, adiomics can uncover the clinical significance behind radiomics features, making them potential biomarkers for early diagnosis, prognosis assessment, and treatment monitoring of HCC. On the other hand, adiogenomics can elucidate the potential biological significance behind imaging features, aiding in the discovery of potential biomarkers. This not only enhances understanding of the occurrence and development of HCC but also provides a basis for individualized treatment decisions. Subsequently, we will elaborate on these points with specific research.

Application of Radiomics in the Detection of Primary/Recurrence HCC and Its Risk Factors

Diagnosis of HCC

Ultrasonography is essential for early screening of HCC,[47] while radiomics shows promise in diagnosing different liver lesions.[48] A meta-analysis comparing the diagnostic accuracy of AI and human experts in identifying liver cysts, hemangiomas, HCC, and hepatic metastases found that AI surpassed human experts in distinguishing these lesions.[49] This conclusion was further supported by another study using Contrast-Enhanced Ultrasound (CEUS) to distinguish between benign and malignant Focal Liver Lesions (FLLs), underscoring AI's immense potential in HCC diagnosis.[50]

Pathological classification of primary liver cancer includes HCC, cholangiocarcinoma, and mixed-cell carcinoma.[51] Accurate pathological subtyping is instrumental in devising appropriate treatment plans. Although pathological results are essential for confirming subtypes, researchers have made strides in pre-surgical diagnosis based on ultrasonography (US) data. In a retrospective study involving 668 hCC patients, Peng and colleagues employed ITK-SNAP to define tumor boundaries on ultrasound images, extracting Regions of Interest (ROIs) and constructing optimal classification models using various dimensionality reduction methods and machine learning models to identify HCC, achieving Area Under Curve (AUC) values of 0.854 and 0.775 in training and validation cohorts, respectively.[52] Further studies have demonstrated the efficacy of ultrasound-based omics models in distinguishing HCC from ICC, with notable AUC values in training and validation sets.[53] Additionally, Li and colleagues developed an ultrasound omics model to differentiate HCC from mixed-cell carcinoma, comparing its performance with CEUS LI-RADS, showing higher AUC, specificity, and sensitivity. However, the differences were not statistically significant.[54]

Although ultrasound (US) remains a common method for screening liver focal lesions (FLL), CT and MRI have higher accuracy in diagnosing HCC, offering significant advantages in identifying metastatic HCC. Dankerl et al have developed a CADx system based on CT, which relies on a random forest similarity model and content-based image retrieval algorithms. When utilizing ROI images alone, the area under the curve for distinguishing between benign and malignant liver tumors is 0.751, which increases to 0.914 when both images and semantic features are used.[55] Suo and others have demonstrated the feasibility of using texture features derived from contrast-enhanced CT (CECT) to differentiate between liver abscesses and malignant mimickers, with an ROC area under the curve of 0.888,[56] highlighting the potential of texture features in predicting HCC. Notably, standardizing the workflow and developing reusable models are crucial for enhancing the reproducibility of this work. To this end, Hu et al have constructed four radiomics models for differentiating necrotic hepatocellular carcinoma (nHCC) from pyogenic liver abscess (PLA) using CECT

images from the arterial and portal venous phases, focusing on the lesion's wall and necrotic cavity, with the R-score (ROI-wall) based on the portal venous phase achieving AUCs of 0.985 and 0.928 in the training and validation cohorts, respectively.[57] Another study constructed a radiomics score based on CT. It combined it with clinical variables to predict hepatocellular adenoma (HCA) and HCC in non-cirrhotic livers, achieving ROC areas under the curve of 0.96 and 0.94 in the training and validation sets, respectively.[58] These reports affirm the positive role of CT-based radiomics in the diagnosis of HCC; similarly, MRI-based approaches can also provide accurate pre-diagnosis of HCC. A study on a Gd-DTPA-enhanced MRI radiomics model showed its accuracy in identifying HCC and focal nodular hyperplasia (FNH) in non-cirrhotic livers to be 0.956 and 0.941, respectively, significantly outperforming clinical models.[59] Another research indicated that an MRI-based radiomics model for differentiating HCC from hepatic hemangioma (HH) performed nearly as well as experienced radiologists.[60] In differentiating HCC from ICC, Wang and colleagues found that an MRI radiomics model demonstrated superior performance in identifying HCC lesions during the delayed phase (AUC = 0.91).[61] These reports underscore the positive impact of radiomics, combined with multimodality medical image, in diagnosing liver cancer, its principal advantage being the quantification of image data over subjective interpretation by radiologists. Naturally, in clinical practice, integrating radiomics with other clinical information is essential for obtaining more reliable diagnostic outcomes.

Prediction of Risk Factors for HCC Recurrence or Metastasis

The five-year recurrence rate of HCC reaches up to 70%, presenting a clinical challenge urgently needing resolution.[62] The recurrence of HCC is associated with various factors such as tumor characteristics, liver function status, pathological types, and treatment conditions. MVI and PVTT have been identified as independent risk factors for early postoperative recurrence of HCC,[63–65] but since PVTT can develop from MVI and its diagnosis relies on imaging studies, and most patients with HCC combined with PVTT are ineligible for surgical treatment, it does not serve well as a predictive outcome for radiomics. Currently, the diagnosis of MVI relies on postoperative pathology. However, radiomics allows for the non-invasive assessment of these risk factors, thus enabling effective interventions to prevent recurrence in early time.[66] A retrospective study involving 482 hCC patients showed that a radiomics score based on enhanced ultrasound contrast is an independent risk factor for MVI, and combining it with alpha-fetoprotein (AFP) and tumor size can further enhance the model's predictive accuracy.[67] Yang et al calculated a radiomics score based on quantitative features from gadolinium-ethoxy benzyl-diethylenetriamine pentaacetic acid MR and constructed a predictive model for MVI, integrating it with clinicoradiological features. This model's AUC in the training and validation cohort was 0.943 and 0.861, respectively, surpassing subjective image feature assessments.[68] In another study based on enhanced CT, researchers constructed R-score and LI-scores to predict MVI, where the R-score was derived from quantified radiomics features, and LI-scores were from radiologists' visual observations of the lesion. The results indicated that the addition of an R-score does not provide a net benefit over LI-scores, and radiomics features were not as crucial in the regression model as radiologists' assessments of factors such as encapsulation, tumor margins, and peritumoral enhancement. Moreover, the model construction method used recursive feature elimination support vector machines (Ref-SVM), differing from previous studies.[69] In selecting classification model methods, typical machine learning models like logistic regression, support vector machines, or XGBoost are primarily used, but some studies also involve deep learning models. Jiang et al compared the predictive efficacy of the Radiomics-Radiological-Clinical (RRC) model and a 3D-CNN model for MVI, showing that the 3D-CNN model's AUC was higher than that of the radiomics model and the RRC model with added clinical features, though without significant difference.[70]

Recent research has identified a novel vascular pattern called VETC that promotes HCC metastasis independently of epithelial-mesenchymal transition (EMT), leading to higher recurrence rates and shorter survival in patients.[71,72] A Gd-EOB-DTPA MRI-based radiomics model can effectively predict VETC occurrence, thus distinguishing recurrence risks complementing tumor region models with peritumoral area models.[73] Dong et al developed a deep learning radiomics model using dynamic contrast-enhanced MRI has been developed to noninvasively evaluate vessels encapsulating tumor clusters (VETC) and predict prognosis in hepatocellular carcinoma (HCC) patients.[74]

Prediction of HCC Prognosis

For Barcelona Clinic HCC (BCLC) early-stage patients, surgery remains the preferred treatment, along with liver transplantation and ablation as significant options.[75] Monitoring and intervening in postoperative recurrence is vital for extending overall survival and improving prognosis. Wu et al included 513 patients treated with Microwave Ablation (MWA), constructing a CNN ResNet 18 model based on ultrasound greyscale images, showing superior performance in predicting early HCC recurrence and cell differentiation.[76] A study utilizing Contrast-Enhanced Ultrasound (CEUS) integrated radiomics (random forest) and deep learning models (support vector machine) achieved AUCs of 0.942 and 0.889 in training and validation sets for predicting early HCC recurrence.[77] Compared to ultrasound, more radiomics research on HCC recurrence prediction is based on CT and MRI. Ji et al developed a model using CT-based radiomics and image features for predicting early recurrence, with postoperation models incorporating pathological features showing more remarkable differentiation ability.[78] CT-based radiomics models also predict recurrence in various treatments.[79–81]

Due to its enhanced sensitivity and specificity, liver MRI has been extensively utilized in HCC radiomics research. Lv et al developed a preoperative model based on HCC MRI to predict aggressive intrasegmental recurrence (AIR) post-radiofrequency ablation (RFA), achieving AUCs of 0.941 (95% CI: 0.876–1.000) and 0.818 (95% CI: 0.576–1.000) in training and validation sets, respectively.[82] Wang and colleagues constructed an imagingomics model for predicting early recurrence in solitary HCCs smaller than 5 cm using Multi-Sequence MR, effectively identifying patients at high risk for early recurrence post-R0 resection.[83] Numerous MRI-based radiomics studies exist, but due to cohort diversity, procedural differences, and equipment variability, the features constructed for radiomics vary. However, the models consistently demonstrate good predictive outcomes for endpoints.[84–86] Compared to MRI contrast agents, Gd-EOB-DTPA is favored by researchers for its unique biological properties that facilitate the qualitative diagnosis and detection of small HCCs. In a study including 167 patients with solitary HCCs of 2–5 cm, Kim et al found a preoperative Gd-EOB-DTPA-enhanced MRI radiomics model, based on a 3mm margin around the tumor boundary, to predict early recurrence of HCC comparably to postoperative pathological models;[87] another study on 158 hCC patients identified rim arterial phase hyperenhancement in Gd-EOB-DTPA-enhanced arterial phase as an independent predictor of proliferative HCC, associated with poorer overall survival and higher extrahepatic metastasis rates.[88] Vessels encapsulating tumor clusters (VETC), an independent risk factor for postoperative recurrence, are closely related to early recurrence of HCC. These findings underscore the importance of peritumoral changes in HCC, which Gd-EOB-DTPA MRI can sensitively capture. Additionally, some MRI-based radiomics studies focus on overall survival, like Wang et al's model on 201 hCC patients predicting 5-year survival rates, with AUCs of 0.9804 and 0.7578 in training and validation sets, respectively.[89] Despite this, more research centers on clinically significant HCC recurrence.

Evaluation of the Effect of Non-Surgical Treatment

For patients unable to receive surgery, immunotherapy represented by anti-PD-1 and PD-L1 has gradually become a new treatment option,[90] and how to evaluate the treatment effect has become a clinical key point. Existing research has shown the advantages of radiomics in evaluating the effectiveness of non-surgical treatment. An ongoing Phase II clinical trial assessed a novel sequential transarterial chemoembolization (TACE) combined with stereotactic body radiotherapy (SBRT) and immunotherapy strategy for treating inoperable HCC patients, demonstrating that four DeltaP-derived radiomic features were correlated with treatment responsiveness at three months.[91] In a multicenter study, Bo and colleagues used a radiomics model to evaluate the treatment response to Lenvatinib monotherapy in inoperable liver cancer, where subtype I was associated with a higher objective response rate (ORR) and longer progression-free survival (PFS).[92] Additionally, a multicenter study indicated that radiomics models could identify patients benefiting from postoperative adjuvant transarterial chemoembolization (PA-TACE), showing a significant reduction in early recurrence rates in the high-risk group with PA-TACE ($p = 0.006$), without significant impact on the low-risk group ($p = 0.270$).[93] Another study displayed the good performance of radiomics models in predicting the treatment response of HCC patients to transarterial embolization (TAE).[94] Based on this, combining clinical features and imaging characteristics can further enhance the predictive performance for the initial TACE response.[95] Radiomics assessments of non-surgical treatment response in HCC patients, such as TACE, are common, and incorporating clinical features can further stratify HCC patients.

The Role of Radiogenomics in HCC

Unique Immune Microenvironment

The occurrence of HCC is a complex process influenced by multiple factors. Despite the existence of over ten clinical staging systems to guide clinical decisions, there is significant prognostic heterogeneity among patients within the same stage.[96] Therefore, more refined stratification methods are required to meet the needs of precision treatment. With the advancement of omics technologies like RNA-seq or scRNA-seq, the development of HCC is understood not as an isolated process but one involving changes in various tumor microenvironment components.[97,98] The HCC immune microenvironment was made up of immunosuppressive cells, immune effector cells, cytokine environments, and inherent tumor cell signaling pathways, with different etiologies influencing the immune response, which lead to unique microenvironmental characteristics.[99,100] Radiomics has shown a close correlation with clinical prognosis and treatment response in HCC. Combined with sequencing technologies, radiogenomics can provide biological annotations for different HCC molecular subtypes, achieving precise stratification of HCC patients for maximal clinical treatment benefits.

Radiogenomics Reveals Prognostic-Related Biological Pathways

Oncogenesis often involves angiogenesis, which plays a crucial role in HCC growth and metastasis. Hence, Bevacizumab, aimed at inhibiting angiogenesis, is utilized as a first-line treatment for advanced, inoperable HCC. Various imaging techniques are now routinely employed to monitor angiogenesis, an essential component of late-stage HCC treatment.[101] Due to the liver's dual blood supply and rich vascularization, it is highly susceptible to MVI. Previous discussions have highlighted radionics advantages in predicting HCC MVI, yet few studies have explored the tumor microenvironment (TME) in MVI patients. To address this, Wang and colleagues incorporated RNA-seq, WES, and scRNA-seq data to analyze the heterogeneity of HCC intrahepatic metastasis (IM) and multicentric occurrence (MO), integrating imaging data to elucidate the biological relevance of radiomic features with the TME. The findings revealed that not only do MVI-positive HCC patients have elevated levels of APOE+ macrophages and iCAFs, but the Radscore used for predicting MVI and prognosis is also highly correlated with the infiltration of APOE+ macrophages and iCAFs.[102] iCAFs may secrete inflammatory factors, causing HCC metastasis and immune escape. This study suggests a non-invasive method for assessing the TME and may provide new insights for HCC treatment.

^{18}F-2-fluoro-2-deoxyglucose (^{18}F-FDG) PET/CT is extensively used for early diagnosis, staging, efficacy evaluation, and prognosis of various cancers, including HCC. The uptake process of FDG by cells mimics glucose glycolysis, with cancer cells utilizing more glucose than normal cells. Hence, metastatic HCC lesions show significantly higher 18F-FDG uptake. An and colleagues explored the molecular mechanisms of 18F-FDG high-affinity HCC, finding the mTOR signaling pathway activated in such HCC cases, associated with poor prognosis, suggesting high aggressiveness of HCC may depend on mTOR's metabolic reprogramming.[103] This study links PET/CT imaging reflecting FDG uptake rates with the glycolytic activity of HCC under hypoxia, further associating the high aggressiveness of HCC with abnormal mTOR activation, thus connecting imaging with transcriptomic information. However, this research approach relies more on different imaging techniques and the development of new contrast agents, generally reflecting only tumor cell uptake, not comprehensively assessing the tumor microenvironment.

Radiogenomics and Immunotyping and Key Genes

CK19, a marker of biliary epithelial cells, has been increasingly evidenced to signify a subtype of HCC originating from hepatic progenitor cells (HPC), characterized by high invasiveness, elevated lymph node metastasis rates, and poor postoperative prognosis. Thus, understanding CK19 status is crucial for HCC treatment. Researchers have developed radiomics models based on Gd-EOB-DTPA-enhanced MRI to identify CK19-positive HCC, with AUCs in training and two validation cohorts being 0.857, 0.726, and 0.790, respectively.[104] Wang et al developed a similar radiomics model predicting CK19 mutation status.[105] TP53 and CTNNB1 are known to be high-frequency driver mutations in HCC and

are closely linked with its onset and progression, with radiomics also predicting the status of these critical mutations, aiding in diagnostic and therapeutic decisions.

Gu et al extracted radiomic features from enhanced CT of HCC patients, developed a Fusion Feature Subtype Model (FIFS) identifying different radiomics subgroups, revealed FIFS-determined subgroups as independent prognostic factors, with heterogeneity mainly from inflammatory pathways and tumor immune environment activation, and confirmed feature-immune pathway correlations.[106] The PI3K pathway plays a significant role in HCC development, with Liao et al extracting features from peritumoral and tumor regions to build models predicting PI3K pathway somatic mutations, indicating machine learning-based radiomic features could characterize PI3K signaling alterations in HCC, potentially identifying sorafenib treatment candidates.[107]

Relationship Between Radiogenomics and Other Genomic Information

Not only mutations of essential genes but also, in recent years, an increasing amount of genomic information have shown great potential in achieving the goal of precision treatment for HCC. For instance, indicators such as Tumor Mutational Burden (TMB), Microsatellite Instability (MSI), and Defective Mismatch Repair (dMMR) have been proven to relate to anti-tumor immune responses.[83] Hence, establishing a connection between these indicators and imaging could noninvasively stratify HCC patients, allowing for the formulation of alternative interventions for patients with poor immune responses to enhance the efficacy of immunotherapy. Moreover, the number of neoantigens is closely related to the efficacy of immunotherapy in HCC patients, with HCC being no exception.[108] Revealing the abundance of neoantigens through imaging represents a potential research direction, though such studies require more advanced methods and technologies for support. Moreover, the development of radiogenomics introduces new perspectives for precision treatment in HCC.

Enhancing Liver Cancer Detection Through Artificial Intelligence

Liver imaging can be optimized through techniques like deep learning-enhanced CAIPIRINHA-VIBE, significantly improving MRI quality and small lesion detection.[109] Vendor-specific deep learning algorithms further enhance liver MRI, aiding in post-treatment hepatocellular carcinoma detection.[110] Both studies confirm deep learning's role in refining MRI image quality and artifact reduction. The widespread use of AI is expected to enable more precise diagnoses in medical imaging.

Challenges in Radiomics and Radiogenomics

Conventional radiomics models usually results from large number of features in a relatively low number of samples, which leads to the overfitting of the model. The methods of deep learning are often considered to be "black box" models and lack interpretability, so the goal of current research is to focus on combining multi-omics methods to make up for this deficiency; Although radiogenomics has an edge in the interpretability of the model, it involves cumbersome steps, and minor tweaks can make a difference in the end result. Therefore, we need more standards like IBSI to improve the repeatability of the whole process.

To overcome these challenges, we propose a workflow for radiogenomics in an ideal situation, and the problems that can be solved (Figure 4). First, differences in the manufacturer, model, imaging technology, image quality, scanning protocol, software, and maintenance of CT and MRI equipment in different medical units can lead to variability in image, which requires standardization and calibration to ensure consistency and reliability of analysis. Prior to radiogenomics analysis, we must have established a correlation between the images and the gene or transcriptome information, and trained a stable and reliable AI model to analyze these raw image results. In the future, an ideal radiogenomics workflow would include a cloud or built-in universal AI model that could analyze scans in real time to provide information about patient diagnosis, prognosis, treatment responsiveness, and more. In addition, additional information on tumor heterogeneity, such as tumor stage grade, mutation site, and immune microenvironment (typing), is included.

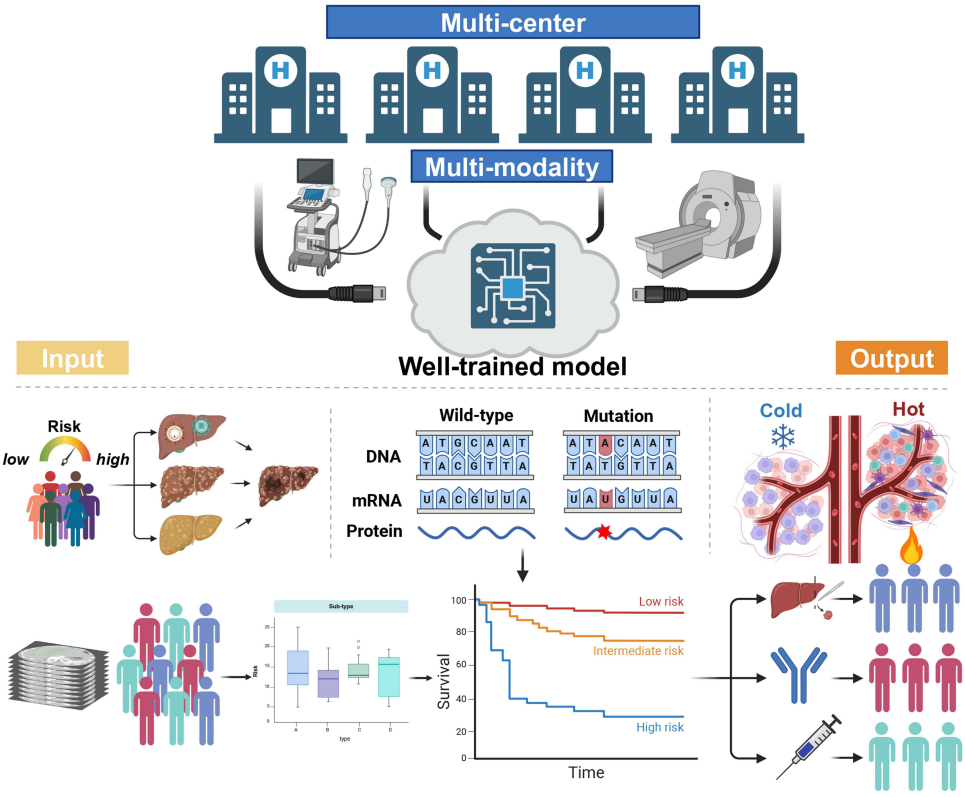

Figure 4 Illustration of future cloud-based processing for radiogenomics. Created in BioRender. 7, R. (2024) https://BioRender.com/a30o348.

Conclusion

Medical imaging is the most common non-invasive diagnostic method for HCC, which provides crucial information on tumor size, edges, and metabolism. This makes imaging an ideal candidate for prognostic information extraction and patient stratification. Radiomics allows for the extraction of quantified features not visible to the naked eye, significantly extending the selection of features available. Radiogenomics bridges the gap between imaging and genetic/transcriptomic information. It characterizing essential genes and pathways through imaging features and providing biological annotations to these features. However, considering the diversity in HCC etiology and genetic information across different populations, there are many challenges in interpreting these connections, assessing the universality. Identifying stable links between imaging and genetic markers across various causes of HCC is a critical issue to be addressed.

In summary, HCC radiomics and radiogenomics have made significant advancements, offering non-invasive and predictive assessment methods. In the future, it is crucial to overcome challenges to provide novel protocol for precise stratification and treatment of HCC patients, which aim to improve prognosis and acquire benefit from imaging information for HCC patients.

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Disclosure

The authors report no conflicts of interest in this work.

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