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REVIEW ARTICLE

The application and challenges of artificial intelligence in imaging-based precision treatment of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the third leading cause of cancer-related deaths worldwide. Early diagnosis and effective treatment of HCC remain major global health challenges and place a significant burden on healthcare systems. In recent years, significant advancements in radiomics and deep learning (DL) technologies have been made in the field of medical imaging, offering new possibilities for the diagnosis, treatment, and prognostic assessment of HCC. This review summarizes the current applications of radiomics and DL in precision medicine for HCC, with a focus on their roles in diagnosis, pathological grading, prediction of microvascular invasion, post-operative recurrence, and treatment efficacy assessment. By analyzing existing studies, this paper demonstrates both the potential and current limitations of these technologies in HCC management and outlines directions for future development.

Keywords: Radiomics; Deep learning; Hepatocellular carcinoma; Precision medicine; Prognosis; Applications and challenges

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the third leading cause of cancer-related deaths worldwide.[1] HCC primarily occurs in patients with chronic liver disease, particularly those with cirrhosis, and its incidence is rising globally. Early diagnosis and treatment are critical for improving patient prognosis. However, due to its insidious onset and rapid progression, most patients are diagnosed at an advanced stage, limiting treatment options and resulting in poor outcomes. Therefore, the exploration of new diagnostic and therapeutic approaches to improve survival rates and quality of life in HCC patients is a key focus of current medical research.[2-4]

In recent years, artificial intelligence (AI) has made significant progress in the medical field, particularly in medical image analysis. AI utilizes machine learning (ML) and deep learning (DL) technologies to automatically learn patterns and rules from large datasets, enabling efficient analysis and interpretation of medical images. The application of AI in medical imaging not only enhances diagnostic accuracy (ACC) and efficiency but

also offers new possibilities for early disease detection, treatment planning, and prognosis assessment.[5,6] In HCC diagnosis, AI technologies can analyze imaging data such as computed tomography (CT) and magnetic resonance imaging (MRI) to automatically extract tumor features, thereby enabling early diagnosis and classification of HCC. In addition, AI can assist in liver tumor segmentation by automatically delineating tumor boundaries, supporting clinical decision-making.[4,7] In recent years, the development of large language models (LLMs) has shown great potential in medical imaging report generation, enabling the automatic generation of structured imaging reports and improving their standardization and readability.[8]

This paper reviews the application of AI technology in the diagnosis, treatment, and prognosis assessment of HCC, with a focus on the roles of radiomics and DL in advancing precision medicine. By analyzing existing research, this paper aims to demonstrate the potential and challenges of AI technology in HCC management and to discuss future directions for its development. Figure 1 shows the application areas, challenges, and prospects of AI in medical imaging for HCC patients discussed in this study.

2. AI technology in the medical imaging of liver cancer

The detailed workflow diagram for applying AI techniques to medical imaging analysis is shown in Figure 2, which provides a comprehensive overview of the general application processes of radiomics and DL in HCC imaging.

2.1. DL

2.1.1. Overview of ML and DL

ML is an important branch of AI that enables systems to automatically learn patterns and rules from data through algorithms, facilitating prediction and decision-making on new data. ML is generally divided into supervised learning, unsupervised learning, and reinforcement learning. Supervised learning trains models using labeled data; unsupervised learning discovers underlying structure in unlabeled data; and reinforcement learning develops optimal behavior strategies through interaction with an environment.

DL, a subfield of ML, focuses on constructing multi-layer neural networks to simulate the information

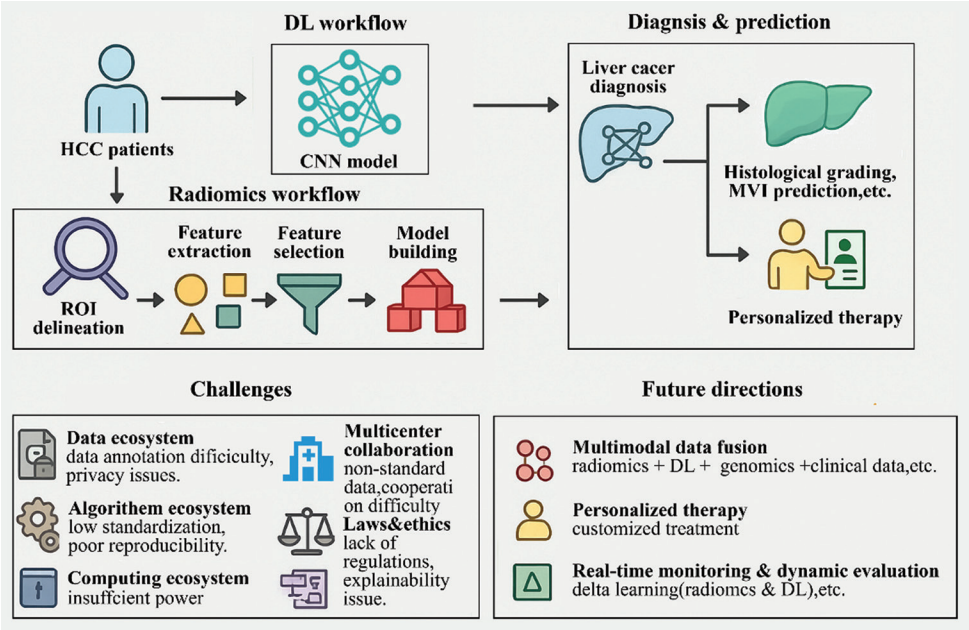

Figure 1. Workflow of HCC-related diagnosis, prognosis prediction using radiomics and DL. The figure shows the process of using radiomics and DL in HCC management. The workflow starts with patient data collection (including imaging and clinical data). In the radiomics workflow, steps include ROI segmentation to model construction. In the DL workflow, the CNN models process image data. Outputs from both workflows support HCC diagnosis and prognosis prediction (such as histological grading and MVI prediction). The figure also highlights current challenges – including data annotation difficulty, low algorithm standardization, and limited computing power – and future prospects such as multimodal data fusion and personalized treatment. Abbreviations: CNN: Convolutional neural network; DL: Deep learning; HCC: Hepatocellular carcinoma; MVI: Microvascular invasion; ROI: Region of interest.

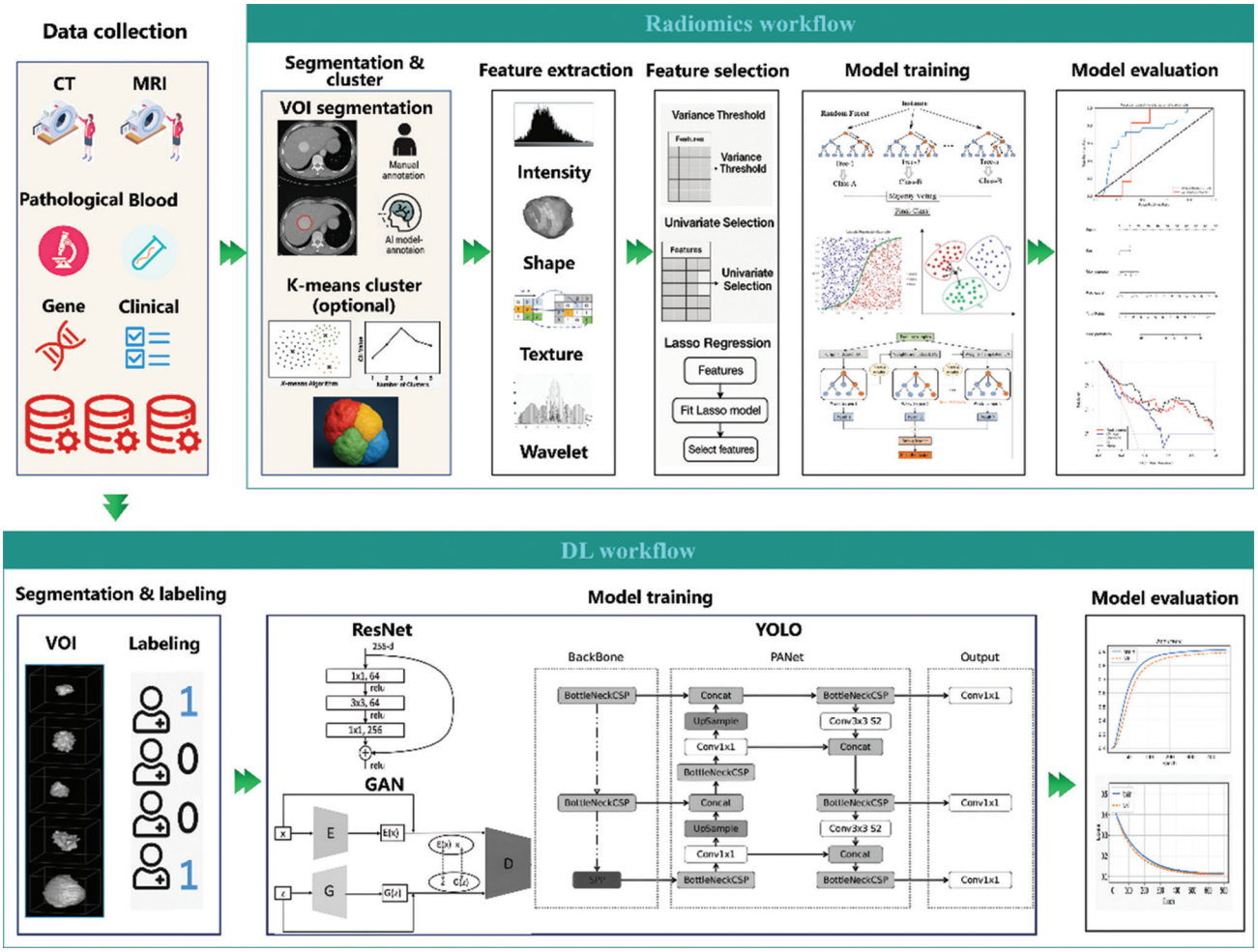

Figure 2. Detailed workflow diagram of AI applications in medical imaging analysis. The figure comprehensively presents the general processes involved in applying radiomics and DL techniques to imaging analysis for HCC. The process starts with data collection, covering imaging modalities such as CT and MRI, along with multi-dimensional clinical data, including pathology, blood test, genomics, and patient records. The radiomics workflow includes segmentation and clustering, followed by feature extraction, feature selection, model training, and model evaluation. The DL workflow includes segmentation and labeling, followed by model training (using neural networks such as ResNet, GAN, and YOLO) and model performance evaluation. This workflow clearly shows the end-to-end application of two AI technologies in medical imaging analysis. Abbreviations: AI: Artificial intelligence; CT: Computed tomography; GAN: Generative adversarial network; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; ResNet: Residual network; SVM: Support vector machine; VOI: Volume of interest; YOLO: You only look once.

processing mechanisms of the human brain. It enables automatic feature extraction and pattern recognition from complex data. These models typically include multiple hidden layers that learn hierarchical representations of data and have achieved significant success in fields such as image recognition, speech recognition, and natural language processing.[9,10]

2.1.2. Neural networks and deep neural networks (DNNs)

Neural networks form the foundational architecture of DL, inspired by the structure and function of biological neurons. A simple neural network consists of an input layer, hidden layers, and an output layer. Each neuron is connected to neighboring neurons through weights and biases. Neural networks compute outputs through forward propagation and update weights through the backpropagation algorithm during model training.

DNNs are advanced forms of neural networks that consist of multiple hidden layers, enabling the model to learn deeper features from the data. DNNs have demonstrated strong performance in demonstrated strong performance image recognition, speech recognition, and natural language processing. Key architectures include convolutional neural networks (CNNs) and recurrent neural networks.

2.1.3. CNNs

CNNs are a classic network architecture used in DL for image processing. Their core components include convolutional layers and pooling layers. Convolutional layers apply filters (kernels) to input images to extract local features, while pooling layers perform down-sampling to reduce the dimensionality of feature maps. This process decreases computational complexity and allows the extraction of increasingly abstract representations.

2.1.4. Generative adversarial networks (GANs)

GANs, introduced by Ian Goodfellow *et al.* in 2014, are DL models designed for image generation. GANs consist of two components: a generator and a discriminator. The generator aims to generate fake images that closely resemble real images, while the discriminator attempts to distinguish between real and fake images. Through adversarial training, where both components are trained simultaneously in opposition, GANs can generate high-quality images.

2.1.5. Large model technology

In recent years, large model technology – particularly LLMs – has made significant progress in the field of natural language processing. These models typically have billions or even trillions of parameters and are capable of learning complex patterns and semantic relationships within language. For example, OpenAI's GPT-4 model demonstrates strong performance in tasks such as natural language generation, text classification, and question answering. Beyond natural language processing, large models have demonstrated great potential in the field of medical imaging. For example, LLMs have been utilized to generate medical imaging reports, improving their standardization and readability.[11]

2.2. Radiomics

As an important subfield of AI in liver cancer imaging, radiomics provides strong support for the diagnosis, treatment, and prognosis assessment of liver cancer by extracting a large number of quantitative features from medical images. It can uncover information not easily visible to the human eye and, when combined with clinical data, allows for the construction of more accurate predictive models. Radiomics thus plays a crucial role in advancing precision medicine for liver cancer.[4]

2.2.1. Radiomics workflow

Region of interest (ROI) delineation is the first and most critical step in radiomics analysis. In liver cancer research, experienced radiologists typically use specialized image analysis software to manually delineate the liver cancer lesions and surrounding tissues on medical images such as CT and MRI scans. This process requires extensive professional knowledge and experience, as the ACC of the delineation directly impacts the quality and reliability of subsequent feature extraction.

Following ROI delineation, the next step is feature extraction. In this stage, specialized software is used to extract various types of features from the ROI to comprehensively describe the imaging characteristics of the tumor. These features mainly include morphological features, histogram features, texture features, and higher-order features. Morphological features describe geometric attributes such as shape, size, volume, and surface area, providing insight into characteristics such as tumor regularity and boundary definition. This information helps determine the malignancy and invasiveness of the tumor. Histogram features reflect the distribution of gray values in the image, such as the mean gray value, standard deviation, skewness, and kurtosis, which can, to some extent, indicate the heterogeneity of the tumor tissue. Texture features quantify the spatial distribution of pixel intensities, capturing subtle internal variations in the tumor. These include features such as contrast, correlation, energy, and entropy, often derived from the gray-level co-occurrence matrix, and are useful for differential diagnosis. Higher-order features involve more complex transformations, such as wavelet transform features and fractal dimensions, which can reveal deeper, less apparent image information.

Since a large number of raw features are extracted from the ROI, many of them may be redundant and irrelevant. This can increase model complexity and training time while reducing generalizability. Therefore, feature selection is necessary. Commonly used feature selection algorithms include recursive feature elimination, analysis of variance, minimum redundancy maximum relevance, and least absolute shrinkage and selection operator regression.

After feature selection, the next step is model construction. Common algorithms used include support vector machines (SVMs), logistic regression (LR), and random forests (RF). The performance of the predictive models is typically evaluated using metrics such as ACC, sensitivity, specificity, the area under the receiver operating characteristic curve (area under the curve [AUC]), and calibration curves.

2.2.2. Emerging radiomics methods

Delta radiomics is an emerging method developed based on traditional radiomics. It focuses on analyzing changes in imaging features before and after treatment to evaluate treatment efficacy and predict disease recurrence. By comparing imaging features from the same patient at

different time points – such as before and following chemotherapy or targeted therapy – delta radiomics can detect dynamic changes in tumor size, shape, texture, and other features. This allows clinicians to assess treatment response more accurately. Compared with traditional radiomics, which relies solely on imaging data from a single time point, delta radiomics offers a more comprehensive understanding of tumor biology and treatment response, thus enabling timely adjustments to therapeutic strategies. However, delta radiomics also faces some methodological challenges, such as the time interval between imaging sessions and the inconsistencies in imaging equipment and acquisition parameters. This may affect the ACC of feature differences and therefore require strict quality control and standardization for reliable application and research.[12]

Habitat analysis radiomics is another novel radiomics approach based on the concept of the tumor microenvironment. The tumor microenvironment – which comprises various components such as tumor cells, immune cells, blood vessels, and extracellular matrix – plays a crucial role in tumor initiation, progression, invasion, and metastasis. Habitat analysis radiomics extracts imaging features related to the tumor microenvironment, such as the complexity of textures surrounding the tumor and vascular distribution characteristics, to gain a deeper understanding of the tumor biology and prognosis. Studies have shown that peritumoral imaging features are closely associated with immune infiltration and angiogenesis within the tumor microenvironment. These features may help in accurately predicting patient outcomes and tailoring personalized treatment strategies. However, habitat analysis radiomics remains in the exploratory phase. Further research is needed to precisely define and extract relevant features and to establish robust correlations with clinical outcomes.[13]

2.2.3. Advantages and disadvantages of various imaging informatics methods

Traditional radiomics offers several advantages, including well-established technology and standardized procedures. It has demonstrated effectiveness in the diagnosis, pathological grading, and assessment of microvascular invasion (MVI) in liver cancer, providing valuable information for clinical decision-making. In addition, it has relatively low data requirements, making it suitable for studies with limited sample sizes. However, traditional radiomics suffers from issues such as feature extraction relying on manual operations, strong subjectivity, and the lack of unified standards for feature selection, leading to poor comparability between different studies and limiting its broader clinical application.

Delta radiomics enables dynamic monitoring of tumor responses to treatment, providing a real-time basis for adjusting personalized treatment plans. It has unique advantages in evaluating treatment efficacy and predicting disease recurrence. However, this method is highly influenced by imaging acquisition conditions and currently lacks standardized analytical protocols and guidelines, resulting in limited reliability and reproducibility of findings.

Microenvironmental radiomics introduces a new perspective on focusing on the tumor microenvironment, offering insights into tumor biology that may improve prognostic ACC and treatment planning. However, current understanding of how imaging features relate to the tumor microenvironment is still limited. In addition, methods for feature extraction and analysis remain underdeveloped, necessitating further basic research and clinical validation to fully realize their potential.

2.3. Model evaluation metrics

2.3.1. AUC

AUC quantifies the model's ability to discriminate between classes across different decision thresholds using true-positive rate (sensitivity) and false-positive rate (1 - specificity). In liver cancer research, an AUC of 1 indicates perfect classification (e.g., complete separation of HCC and hepatic cysts), while an AUC of 0.5 suggests predictive ability equivalent to random guessing. Typically, an AUC ≥0.9 is considered excellent (e.g., multimodal imaging combined with clinical indicators for predicting MVI), 0.75 – 0.9 indicates moderate performance, and AUC <0.75 suggests the need for feature or algorithm optimization. AUC is commonly used in scenarios such as recurrence risk stratification and vascular invasion prediction.

2.3.2. ACC

ACC calculates the proportion of correctly predicted samples out of the total number of samples (ACC = [true positives + true negatives]/total samples), reflecting the model's overall predictive correctness. However, in imbalanced datasets – common in liver cancer research (e.g., recurrence cases comprising only 10%) – ACC can be misleadingly high due to dominance by the majority class. For example, 90% normal samples would yield 90% ACC even if all positive cases are missed. Therefore, ACC should be interpreted alongside sensitivity and specificity. In clinical research, it is often used for initial model screening, typically in combination with cross-validation to improve reliability.

2.3.3. Sensitivity and specificity

Sensitivity, or the true-positive rate, refers to the proportion of actual positive cases correctly detected by the model (sensitivity = true positives/[true positives + false negatives]). In the early diagnosis of liver cancer, high sensitivity (≥0.85) is crucial to reduce the missed diagnosis of small lesions or early recurrence.

Specificity, or true negative rate, represents the proportion of actual negative cases correctly excluded (specificity = true negatives/[true negatives + false positives]). High specificity (≥0.8) is clinically crucial for mitigating false-positive results and precluding unnecessary invasive interventions in benign cases.

2.3.4. F1 score

The F1 score balances the model's ability to identify positive and negative samples by taking the weighted average of precision (positive predictive value [PPV] = true positives/[true positives + false positives]) and recall (sensitivity). It is calculated as F1 = 2 × (PPV × recall)/(PPV + recall). It is particularly useful in detecting rare events – such as liver cancer micrometastases or recurrence within 3-month post-surgery – where the F1 score better reflects a model's ability to identify minority classes compared to ACC. An F1 score ≥0.7 is typically indicative of strong discriminative performance.

2.3.5. Kappa coefficient

The Kappa coefficient measures the agreement between model predictions and ground truth, adjusted for chance agreement (Kappa = [observed agreement − expected agreement]/[1 − expected agreement]). In liver cancer segmentation tasks – such as delineation of liver lobes or tumor boundaries – a Kappa ≥0.7 indicates high consistency with manual annotations, supporting the reliability of automated segmentation tools. A Kappa near 0 suggests performance equivalent to random guessing, warranting algorithm refinement.

2.3.6. Confidence interval (CI)

CIs quantify the statistical uncertainty of model evaluation metrics (e.g., AUC and ACC), typically presented as a 95% CI (e.g., AUC = 0.85, 95% CI: 0.80 – 0.90). In a multicenter study of liver cancer, a CI variation ≤5% across cohorts indicates strong generalizability; conversely, a wide CI may indicate sample heterogeneity or insufficient data, requiring a larger sample size or adjustment of the feature set.

2.3.7. Youden index

The Youden index is calculated as sensitivity + specificity - 1 and is used to determine the optimal threshold that balances false negatives and false positives. In clinical decision-making for liver cancer, thresholds derived from the Youden index can help guide risk stratification (e.g., imaging score ≥X indicates high recurrence risk), reducing both overtreatment and missed diagnoses caused by arbitrary threshold selection.

3. Application of radiomics and DL in liver cancer

3.1. Application research in liver cancer lesion segmentation

Liver tumor segmentation is the foundation of liver imaging research and a critical step in visualizing liver anatomy to support surgical planning. Precise 3D visualization assists surgeons in assessing tumor size, volume, and resection range, ensuring an appropriate post-operative liver residual ratio. Manual segmentation based on imaging is cumbersome, while automatic segmentation is challenging due to blurred boundaries between tumors and healthy tissue, CT noise artefacts, and tumor heterogeneity. Despite these challenges, automated methods offer the advantages of objectivity, reproducibility, and reduced reliance on human labor. Alirr *et al.*[14] proposed a fully automated tumor segmentation technique based on enhanced CT images. This method involves enhancing tumor contrast using anisotropic filtering, generating an initial tumor mask through adaptive thresholding, and refining the boundary using a local level set-based active contour algorithm. The method was validated in a professional dataset, and core metrics – including dice similarity coefficient (DSC) and absolute relative volume difference – demonstrated ACC comparable to expert manual annotations. Traditional medical image segmentation methods include thresholding, region growing, edge detection, and clustering. However, DL approaches, particularly CNN and UNet-based variants, have significantly improved segmentation ACC through end-to-end learning, making it easier to distinguish hepatic lesions and aiding in precise treatment planning.

Zang *et al.*[15] developed a UNet variant model that first enhances image quality using adaptive filtering through a pulse-coupled neural network, then embeds a squeeze-and-excitation module into a residual network, and finally, connects this with a UNet architecture through bilinear interpolation to complete the segmentation. Validation on a multicenter dataset showed that, compared to the original UNet model, this enhanced network significantly improved key segmentation evaluation metrics, optimizing overall performance.

Another proposed method involves an automatic two-step liver and tumor segmentation process using a cascaded

framework.[16] First, FRA-UNet is used to localize and preliminarily segment the liver. Then, the same network is applied to predict liver tumors within the ROIs. Finally, a 3D conditional random field (CRF) is employed to refine tumor segmentation. The improved feature reuse structure and deep residual blocks enhance feature extraction, while the 3D CRF improves contour smoothing. When tested on two professional datasets, FRA-UNet achieved DSCs of 97.13% and 97.18% for liver segmentation and 71.78% and 68.97% for tumor segmentation – outperforming most advanced networks. DL-based tumor segmentation automatically extracts multi-scale semantic features through an end-to-end network, combined with residual connections and attention mechanisms to enhance feature expression. This approach effectively addresses issues such as variable tumor morphology and blurred boundaries, offering significant advantages over traditional methods (e.g., threshold segmentation, region growing) in terms of segmentation ACC, robustness, and automation.

3.2. Application of radiomics and DL in the diagnosis and classification of HCC

The early and accurate identification of HCC plays a critical role in clinical intervention and disease prognosis. Unlike most solid tumors that typically require histopathological diagnosis, HCC can often be clinically diagnosed based on its typical imaging features, without the need for histopathological verification.[17] However, certain benign liver tumors exhibit imaging features that closely mimic HCC, posing significant challenges for differential diagnosis using conventional imaging techniques and thereby placing high demands on diagnostic ACC.[18] In recent years, radiomics techniques based on ultrasound, CT, and MRI have enabled the extraction of deep features such as lesion texture and heterogeneity to construct data models. These quantitative features demonstrate high efficacy in the differential diagnosis of HCC from other liver lesions such as focal nodular hyperplasia (FNH), hepatocellular adenoma (HCA), and intrahepatic cholangiocarcinoma (ICC), thereby providing objective quantitative evidence for distinguishing between benign and malignant hepatic lesions.

Approximately 30% of patients with cirrhosis eventually progress to HCC.[19] Given the high incidence of cirrhosis and the poor prognosis of HCC, the two conditions together constitute a major public health challenge. Mokrane *et al.*[21] conducted a multicenter retrospective study of 178 patients with cirrhosis and uncertain liver nodules. They extracted high-throughput radiomics features from three-phase dynamic contrast-enhanced CT images and found that a model based on arterial and portal venous phase changes demonstrated optimal performance in distinguishing HCC from non-HCC lesions. Guo *et al.*[22] conducted a large-scale study involving 1,858 cirrhotic patients across 11 centers, collecting three-phase CT images and laboratory data 3 – 12 months before either HCC diagnosis or final follow-up. They integrated clinical scores (including aMAP, age, sex, total bilirubin, albumin, platelet count, and alpha-fetoprotein [AFP]), imaging-based radiomics scores, and DL scores into an LR model known as ALARM. This model achieved AUCs of 0.929, 0.902, and 0.918 in the training, internal validation, and external validation sets, respectively, highlighting the potential of radiomics as an early warning tool for HCC development in cirrhotic patients.

Most HCC cases are caused by hepatitis B, hepatitis C, or alcohol abuse,[22] but approximately 12% cases occur in patients without cirrhosis.[23] The differential diagnosis of non-cirrhotic HCC is particularly challenging due to the lack of typical clinical features and its resemblance to benign lesions such as HCA, FNH, and well-perfused benign tumors like lipomatous hepatic angiomyolipoma. Nie *et al.*[24] extracted a large number of imaging features from contrast-enhanced phase-three CT images, screened them, and ultimately included seven imaging features to calculate an imaging score. This score was combined with independent clinical factors and analyzed using multiple LRs to construct an imaging nomogram. This model showed great potential in distinguishing HCA from HCC. Ding *et al.*[25] reported that a combined model incorporating radiomics features from the arterial and portal venous phase of MRI with GD-DTPA contrast enhancement, along with clinical features, demonstrated excellent performance in distinguishing HCC from FNH in non-cirrhotic patients, with an AUC of 0.984 in the training set. Similarly, Zhao *et al.*[26] demonstrated that a radiomics model based on three-phase contrast-enhanced MRI can assist in distinguishing HCC from angiomyolipoma, with an AUC of 0.789 in the training set. The model was validated across multiple centers and performed on par with, or better than, experienced radiologists. Hamm *et al.*[27] trained a customized CNN using 494 multimodal MRI images of liver lesions, classifying them into six categories – simple cyst, cavernous hemangioma, FNH, HCC, cholangiocarcinoma, and colorectal cancer metastasis – with high diagnostic performance.

The major pathological types of primary liver cancer primarily include HCC, ICC, and combined HCC-ICC.[28] Given the differences in malignant potential and treatment approaches for these subtypes,[29] accurate classification is crucial for optimal patient management. Lewis *et al.*[30] found that the combined use of quantitative histogram analysis from diffusion-weighted MRI and the liver

imaging reporting and data system grading can improve the differentiation between HCC and other primary liver malignancies. Wang *et al.*[31] manually delineated tumor regions on MRI, extracted radiomics features, and applied a two-stage feature selection method followed by an SVM classifier. Their model effectively distinguished cHCC-ICC, HCC, and ICC, with seven of the eight selected features being high-order features, highlighting their superior discriminative power. Liu *et al.*[32] combined radiomics features extracted from MRI and CT images with ML to develop a classification model that showed strong predictive performance in differentiating cHCC-ICC from both HCC and ICC.

3.3. Application of radiomics and DL in predicting HCC pathological grading

Pathological grading is an important prognostic factor in HCC and is closely associated with tumor recurrence.[33] Low-grade HCC is more likely to recur early and has a lower overall survival rate compared to higher-grade tumors.[34] To mitigate recurrence risk, extended surgery or adjuvant therapy is often recommended, along with enhanced post-operative monitoring.[35,36] Conventionally, pathological grading relies on post-operative histopathological examination of surgical specimens, which may lead to delays in treatment adjustments. Therefore, pre-operative assessment of tumor grading is of great significance for informing clinical treatment strategies and post-treatment surveillance.

To classify patients into low-differentiation and non-low-differentiation HCC groups, Hu *et al.* incorporated three ML algorithms (i.e., LR, SVM, and Adaboost), building a radiomics-based prediction model using MRI images. The study confirmed that AFP is the only clinical indicator significantly associated with the pathological grading of HCC. The combined model, integrating AFP with radiomics features, demonstrated good diagnostic performance in predicting tumor grade.[37]

In another study, clinical risk factors and MRI features from the arterial, hepatobiliary, and combined imaging phases were incorporated into artificial neural networks (ANN) and LR models to predict high-grade and low-grade HCC.[38] Both models achieved good performance, with the ANN outperforming the LR model in histological grading prediction. Further research has explored the use of multiparametric models built from multiple MRI phases to assist in the preoperative diagnosis and grading of HCC.[39] These models provide valuable insight into the biological characteristics of tumors and enhance clinical decision-making.

Recognizing the limitations of models focused solely on tumor regions, Wei *et al.*[40] developed a DL-based, multi-region imaging model that integrates both tumor and peritumoral imaging features to predict HCC grade. Their findings support the notion that peritumoral regions – reflecting the tumor microenvironment – contain biologically relevant information associated with histological differentiation and may serve as critical indicators of tumor aggressiveness. These studies collectively underscore the utility of multimodal MRI – incorporating T1-weighted, T2-weighted, diffusion-weighted imaging, and dynamic contrast-enhanced sequences – in capturing the heterogeneity of HCC. For example, diffusion-weighted imaging assesses cell density, dynamic enhancement analysis evaluates blood supply differences, and T2-weighted imaging can identify tumor-peripheral edema. The integration of these sequences through radiomics allows for the extraction of comprehensive quantitative features. When combined with clinical variables in predictive modeling, this multimodal approach enables more accurate pre-operative assessment of HCC pathological grade, ultimately supporting the development of personalized treatment strategies.

3.4. Application of radiomics and DL in HCC MVI

MVI refers to the microscopic invasion of tumor cells into small vascular structures such as the portal vein, hepatic artery, or lymphatic vessels. It is commonly observed in the tumor capsule or adjacent hepatic tissue near portal vein branches and is difficult to identify using conventional imaging modalities.[41] MVI status is of great clinical importance as it reflects tumor invasiveness and is a key assessment indicator for predicting post-operative recurrence and clinical treatment decisions in HCC.[42] Hu *et al.*[43] demonstrated that tumor size can be used for pre-operative prediction of MVI in HCC. Similarly, Xu *et al.*[44] demonstrated that imaging features based on contrast-enhanced CT can effectively predict the MVI status of HCC preoperatively and that combining clinical risk factors and imaging features can further improve the predictive performance. Meng *et al.* developed a multimodal radiomics fusion model by extracting features from multiple MRI sequences (arterial phase, delayed phase, diffusion-weighted imaging, and fat-suppressed T2-weighted imaging). Their fusion model achieved good predictive performance, outperforming single-modality models.[45]

In another study, Song *et al.*[46] proposed a DL method based on multimodal MRI, constructing a multi-branch architecture comprising eight independent CNNs. By utilizing multiparameter MRI features such as diffusion-weighted images with different b-values and apparent diffusion coefficient maps, they established a quantitative prediction model for MVI. The study adopted a multi-

source data fusion strategy to optimize the feature space between deep imaging features and clinical risk factors, forming a joint diagnostic model. Results showed that the single radiomics model achieved an AUC value of 0.915 in the test set, while the joint model improved the AUC to 0.931, demonstrating the complementary value of clinical and imaging indicators.

Xia *et al.*[47] extracted radiomics features from multi-phase contrast-enhanced CT images of both tumor and peritumoral regions, combining radiomics scores with clinical risk factors to construct a nomogram. The model achieved an AUC of 0.76 in the training cohort. While the aforementioned studies were retrospective, they provided valuable insights into MVI prediction. However, prospective studies are more robust for clinical translation, as they allow for pre-operative MVI determination to guide surgical decisions – such as wide-margin resection or vascular ligation – and post-operative targeted therapies, including lenvatinib or programmed death-1 inhibitors, thereby optimizing intervention timing and improving patient outcomes.

Dong *et al.*[48] established and evaluated an ML model based on grayscale and Sonazoid contrast-enhanced ultrasound images. Radiomics features were extracted from ROIs of liver cancer lesions and peritumoral tissue, and they were integrated with clinical variables to construct an MVI prediction model. The results showed that the model based on Kupffer-phase images achieved an AUC value of 0.804, outperforming grayscale ultrasound and demonstrating significant clinical value for pre-operative identification of high-MVI-risk liver cancer patients. Jiang *et al.*[49] constructed XGBoost and DL predictive models based on CT images, integrating imaging features and clinical key factors to achieve precise pre-operative MVI prediction, with an AUC value of 0.952. The authors recommended targeted treatment approaches (e.g., anatomical resection or a 0.5 – 1 cm ablation margin) for MVI-positive patients. In addition, the study found that MVI status is an important variable in liver transplantation assessment. With a similar objective, Feng *et al.*[50] used radiomics features from both intra-tumoral and peritumoral regions of contrast-enhanced MRI. Their model achieved an AUC value of 0.85. The study also found that, compared with MVI-negative patients, MVI-positive patients had larger tumor diameters and higher serum AFP levels.

Building upon prior findings, Xu *et al.*[51] combined enhanced CT imaging features with clinical indicators (e.g., AST levels, tumor number, and AFP) to develop a nomogram for MVI prediction. This model stratified patients by recurrence and mortality risk, guiding high-risk individuals toward more aggressive surgery and adjuvant treatment, while enabling low-risk patients to undergo extended surveillance intervals, thus optimizing treatment and follow-up strategies.

In summary, existing radiomics-based MVI prediction models have demonstrated high predictive performance. These models offer objective, non-invasive tools for precision diagnosis and personalized treatment planning in HCC, with the potential to reduce post-operative recurrence and improve patient outcomes.

3.5. Application of radiomics and DL in predicting early tumor recurrence after HCC surgery

For early-stage liver cancer patients with good liver function, radical surgical resection remains the primary treatment option.[52] However, the recurrence rate after the surgery remains high – reaching 70% – leading to poor prognosis.[53] Early tumor recurrence after surgery is one of the most important factors influencing prognosis.[54] It is defined as recurrence within 1 – 2-year post-surgery, with the 1st year being the peak period for liver cancer recurrence.[55] Its risk is associated with tumor pathological characteristics, such as MVI and histological grading,[56] which can be assessed through pre-operative biopsy. However, traditional histopathological examinations are invasive procedures associated with risks such as bleeding and needle tract metastasis and are limited by the spatial heterogeneity of the sampling area, which can lead to misjudgments in pathological grading. In contrast, radiomics features and DL algorithms offer non-invasive assessment techniques that quantitatively reveal tumor heterogeneity characteristics.

Cao *et al.*[57] retrospectively included 127 patients who underwent surgical resection for primary HCC, extracted radiomics features from the maximum cross-sectional images of 2D ultrasound, and constructed three models to predict early recurrence after HCC surgery. Among these, the clinical ultrasound radiomics combined model achieved the best predictive performance. Qian *et al.*,[58] based on radiomics features from multi-phase enhanced CT images, constructed five ML models (including SVM, RF, and K-nearest neighbor [KNN]). Among these, the radiomics model established using SVM achieved the best diagnostic performance, while KNN was the optimal method for constructing a combined model. Xu *et al.*[59] argued that tumor ROIs alone cannot provide global spatial localization information for liver tumors. Therefore, the researchers used a deep CNN to extract deep features from liver CT images with tumor masks to predict early recurrence of HCC. Clinical data were then integrated to further enhance the model's predictive capability. Wang *et al.*[60] conducted a retrospective analysis of 175 patients

with solitary HCC (diameter ≤5 cm). Tumor volumes during the arterial and portal venous phases were segmented, and additional 5 mm and 10 mm margins were defined as peritumoral volumes of interest. Results showed that imaging features from the 5 mm margin region significantly improved the prediction of early recurrence, while the margin beyond 5 mm did not yield further benefit. Furthermore, a multi-phase model combining the arterial and portal venous phases demonstrated superior predictive performance compared to the single-phase models.

A multicenter study further explored the predictive value of contrast-enhanced MRI by extracting both radiomics and DL features.[61] It developed three models – radiomics-only, DL-only, and combined. All models performed well, but deep features showed a significantly higher correlation with ER.

Previous studies largely focused on ER prediction without stratifying patient risk. Wu *et al.*[62] addressed this by retrospectively analyzing enhanced CT images from 132 HCC patients who underwent resection. They integrated radiomics features, Edmondson grade, and tumor size to construct a nomogram for ER prediction. This enabled precise high/low risk stratification, with a significant difference in recurrence risk ($p<0.001$) and an AUC of 0.907 in the training set, thus offering valuable support for clinical decision-making.

Recent advancements in imaging informatics and DL-related studies have shifted toward analyzing tumor peripheries, considering tumor volumes within specific size ranges, and integrating multi-modal features. Studies increasingly apply diverse ML methods or improved DL algorithms to enhance predictive ACC. These efforts provide a new direction for non-invasive prediction of early recurrence after liver cancer surgery. By integrating multi-modal radiomics and DL features, clinicians can implement individualized monitoring and intensive treatment for high-risk patients, thereby advancing precision and personalized therapy.

3.6. Application of radiomics and DL in evaluating the efficacy of hepatic artery chemoembolization therapy for HCC

HCC has an insidious onset and non-specific early symptoms, with approximately 60 – 70% of patients presenting at diagnosis in the advanced stages, having lost the opportunity for curative surgery and requiring palliative treatment.[63] For patients who cannot tolerate surgery or have contraindications, guidelines recommend non-surgical treatment options, including transcatheter arterial chemoembolization (TACE), local ablation (i.e., radiofrequency, microwave therapy, and cryotherapy), radiotherapy, and systemic therapy (i.e., targeted therapy and immunotherapy).[64] TACE is currently the most commonly used non-surgical treatment method,[62] which can effectively inhibit disease progression, prolong survival, and improve quality of life by combining tumor embolization with local chemotherapy.[30,65] However, treatment responses vary among individuals, and early efficacy assessment is critical for optimizing treatment strategies.

Fan *et al.*[66] extracted quantitative texture features from the arterial and venous phases of liver images – obtained 7 days before TACE treatment in patients – and combined radiomics scores and clinical factors to construct a nomogram for predicting the early efficacy of TACE in HCC. The AUC value of the training set was 0.881. Zhang *et al.*[67] developed an ML model based on CT radiomics (features derived from the arterial, venous, and delayed phases) to predict the initial objective efficacy of TACE for HCC, showing promising results. Luo *et al.*[68] integrated multimodal MRI radiomics features with clinical indicators to construct a disease progression prediction model for TACE combined with lenvatinib in the treatment of advanced unresectable HCC. The combined model showed significantly superior predictive performance (AUC = 0.71) compared to the single-feature models, thus providing a non-invasive quantitative tool for dynamic monitoring of treatment response and adjustment of combination therapy. Zhao *et al.*[69] conducted an enhanced MRI imaging analysis to systematically evaluate the predictive value of intratumor and peritumor region (3 mm, 5 mm, and 10 mm) features for TACE treatment response. When the AUC was compared, the model using a 3 mm peritumoral region demonstrated the best predictive performance among the single models, while among the comprehensive models, combining intratumor features, 3 mm peritumoral features, and clinical parameters was the best (validation set AUC = 0.918). In addition, the study confirmed that radiomics features have independent predictive value for tumor recurrence and patient survival after TACE. Kuang *et al.*[70] retrospectively collected MRI images and clinical data from 153 patients with pre-TACE tumor diameters of less than 5 cm across multiple centers. They combined features derived from T2-weighted imaging and dynamic contrast-enhanced MRI with clinical parameters to predict patients' short-term response after TACE. The model achieved an AUC of 0.8 in the training set.

Radiomics has demonstrated promising clinical potential in evaluating treatment efficacy and predicting disease progression after TACE in HCC. However, further research is needed to explore its depth. Future studies should focus on the application of radiomics in a multidisciplinary,

comprehensive treatment setting. This includes developing efficacy prediction models for combined therapies (i.e., TACE with targeted or immunotherapy), conversion therapies (surgery after downstaging), and neoadjuvant therapies (pre-operative bridging). Such models could be enhanced by integrating multimodal imaging features – such as dynamic enhancement and tumor microenvironment – with biological markers (e.g., circulating free DNA, programmed death-ligand 1 expression), enabling a quantitative assessment of tumor heterogeneity and treatment response variability. This approach may provide a foundation for the development of personalized treatment strategies.

3.7. Application of radiomics and DL in predicting survival

Accurate prediction of post-operative survival in liver cancer can optimize treatment intensity, reduce medical resource consumption, and the socio-economic burden. Compared with traditional clinical indicators, radiomics and DL integrate multi-dimensional features to optimize prognosis stratification, holding great potential for evidence-based treatment decisions. A study proposed an integrated learning method based on CT multi-phase enhancement imaging features and clinical data to construct multiple models for predicting the 3-year recurrence-free survival rate of HCC patients, with the best AUC value reaching 0.835.[71] Another study integrated MRI radiomics features with independent clinical risk factors (i.e., AFP and AST) and used RF to construct a predictive model for the 5-year survival rate of HCC patients. The AUC value of the training set reached 0.98, confirming the model's strong potential for prognosis stratification.[72]

In addition to the MVI status, Zhang *et al.*[73] highlighted that vessels encapsulating tumor clusters (VETC) are also closely associated with patient prognosis. Their study combined VETC and MVI with MRI DL radiomics methods to assess recurrence-free survival in HCC patients after liver resection. Stereotactic body radiation therapy (SBRT) is an image-guided precision radiation therapy technique that maximizes the protection of normal liver tissue and has a significantly lower risk of complications than traditional radiation therapy. Chen *et al.*[74] integrated traditional manual radiomics features, DL features, and clinical characteristics to predict the overall survival in HCC patients undergoing SBRT, achieving an AUC value of 0.86. Liu *et al.*[75] integrated texture features derived from enhanced CT with clinicopathological factors to construct a radiomics nomogram predicting the overall survival after liver resection, demonstrating good ACC. Table 1 shows a summary of applications of DL and image informatics in HCC, ensuring consistency with the revised heading.

4. Current challenges and future perspectives

DL and radiomics technologies, through non-invasive, multi-dimensional image feature analysis, have demonstrated the ability to reveal the heterogeneity and invasive biological behavior of HCC. These technologies have made good progress in clinical applications such as diagnosis, classification, pathological grading, treatment response evaluation, and prognosis. However, their clinical translation still faces several shortcomings.

The main bottleneck in current liver cancer radiomics research is the lack of a standardized workflow for the entire process. This includes inconsistent image acquisition parameters (e.g., variation in MRI sequence), differences in pre-processing methods (e.g., slice thickness registration, ROI delineation standards), diverse feature extraction algorithms (e.g., discrepancies in filtering parameters or texture definition), and heterogeneity in modeling strategies (e.g., feature selection thresholds, ML framework). This methodological variability significantly compromises reproducibility and cross-center generalization of findings, with many models validated only in single-center datasets. There is an urgent need to establish internationally recognized technical standards and open-source toolchains to enhance the research comparability and facilitate clinical translation.

Current radiomics studies still largely rely on manual ROI delineation – particularly for tumors with blurred or heterogeneous boundaries – resulting in substantial inter-observer variability and reduced reproducibility. Manual feature extraction, grounded in prior knowledge, builds complex quantification systems, whereas DL enables end-to-end feature learning but is limited by the lack of large, high-quality annotated datasets. Both approaches face challenges in generalizability across centers. Future efforts should focus on developing automated frameworks based on weakly supervised or self-supervised learning and on improving algorithm robustness through multi-center, large-sample validation.

The liver is prone to intrahepatic metastasis, and many patients present with multiple lesions. However, most current radiomics research focuses on single-lesion ROI analysis, overlooking the intrahepatic tumor heterogeneity present in multifocal liver cancer. This remains an important area for future research.

A significant portion of existing studies is retrospective and single center and involves small sample sizes. Thus, further validation through multi-center, large-sample prospective studies is needed.

With the continuous development of AI technology, several future directions are anticipated. Future research will

Table 1. Application of DL and image informatics in HCC

Utility	Image source	Sample size (*n*)	Method	Result	References
Differential diagnosis of HCC in cirrhosis	CECT	HCC: 142; Validation: 36	ML (KNN, SVM, RF)	AUC=0.70	4
Differential diagnosis of HCC in cirrhosis	CECT	HCC: 1145; Validation: 703	DL/ML	AUC=0.929	5
Differential diagnosis of HCC and HCA in non-cirrhosis	CECT	HCC: 85; FNH: 46	ML	AUC=0.96	8
Differential diagnosis of HCC and FNH in non-cirrhosis	CEMRI	HCC: 149; FNH: 36	LR	AUC=0.984	9
Differential diagnosis of HCC and fat-poor AML in non-cirrhosis	CEMRI	HCC: 110; AML: 55	ML	AUC=0.789	10
Classification of six common hepatic neoplasms	CEMRI	494	DL	ACC=0.987	11
Differentiation of HCC from other primary liver malignancies	MRI (ADC map)	HCC: 36; ICC: 17; HCC-ICC: 12	-	AUC=0.90	14
Classification of HCC, ICC, and HCC-ICC	CT and MRI	HCC: 37; ICC: 24; HCC-ICC: 24	ML (SVM)	AUC=0.77 – 0.81	16
Histopathological grade	CEMRI	403	ML (LR, SVM, Adaboost)	AUC=0.70	21
Histopathological grade	CEMRI	122	DL	AUC=0.792 – 0.941	22
Histopathological grade	CEMRI	277	-	AUC=0.95	24
MVI status	CEUS	482	ML (SVM)	AUC=0.731	27
MVI status	CECT	495	-	AUC=0.90	28
MVI status	CEMRI	174	ML	AUC=0.945	29
MVI status	CEMRI	601	DL	AUC=0.931	30
MVI status	CECT	918	-	AUC=0.85	31
Early post-operative recurrence	US and CEUS	127	ML	AUC=0.925	37
Early post-operative recurrence	CECT	214	ML	AUC=0.726 – 0.945	38
Early post-operative recurrence	CECT (peritumoral, tumor<5 cm)	175	-	AUC=0.837	40
TACE treatment response	CECT	108	ML	AUC=0.86	48
TACE treatment response	CEMRI (peritumoral: 3 mm, 5 mm, 10 mm)	138	ML (GBDT)	AUC=0.782 – 0.918	50
TACE treatment response	CEMRI (tumor<5 cm)	153	-	AUC=0.83	51
Recurrence-free survival within 3 years after surgery	CECT	105	ML (LightGBM, CatBoost, XGBoost, GBDT)	AUC=0.734 – 0.833	52
5-year survival rate prognostication	CEMRI	201	ML (RF)	AUC=0.980	53
Evaluating recurrence-free survival	MRI	398	DL	C-index=0.86 (1 year), 0.80 (2 year), 0.87 (3 year)	54
Overall survival after surgery	CECT	544	-	C-index=0.747	56

Abbreviations: ACC: Accuracy; ADC: Apparent diffusion coefficient; AML: Angiomyolipoma; AUC: Area under the curve; CECT: Contrast-enhanced computed tomography; CatBoost: Categorical boosting; CEMRI: Contrast-enhanced magnetic resonance imaging; CEUS: Contrast-enhanced ultrasound; FNH: Focal nodular hyperplasia; GBDT: Gradient boosting decision tree; HCA: Hepatocellular adenoma; HCC: Hepatocellular carcinoma; HCC-ICC: Combined hepatocellular-cholangiocarcinoma; ICC: Intrahepatic cholangiocarcinoma; KNN: K-nearest neighbor; LightGBM: Light gradient boosting machine; LR: Logistic regression; MVI: Microvascular invasion; RF: Random forest; SVM: Support vector machine; TACE: Transarterial chemoembolization; US: Ultrasound; XGBoost: Extreme gradient boosting.

increasingly focus on integrating radiomics with other omics data – such as genomics, proteomics, and metabolomics – to more comprehensively capture the biological characteristics of liver cancer. This multimodal fusion is expected to enhance the ACC of diagnosis, treatment selection, and prognosis assessment. AI-driven radiomics will enable real-time monitoring of treatment response, allowing clinicians to make timely adjustments to therapy. For example, "Delta radiomics," which analyzes changes in imaging features before and after treatment, offers the potential for dynamic assessment of tumor response and can support timely, evidence-based clinical decisions. The integration of AI into liver cancer research will foster collaboration among various disciplines, including medical imaging, oncology, computer science, and bioinformatics. Such interdisciplinary synergy will be essential in driving both scientific innovation and clinical practice forward in liver cancer management.

5. Conclusion

Although DL and radiomics have demonstrated significant value in the non-invasive diagnosis and precise assessment of liver cancer, their clinical translation remains limited by core challenges such as methodological heterogeneity, high reliance on human expertise, and inadequate analysis of multifocal tumor heterogeneity. Future efforts should focus on establishing a standardized workflow encompassing image acquisition, feature extraction, and model validation; developing weakly supervised or self-supervised algorithms to reduce reliance on manual annotations; and validating model generalization through large-scale, multicenter prospective studies. Integrating multi-modal omics data with dynamic Delta radiomics analysis – alongside AI-driven real-time monitoring technologies – holds promise to overcome the limitations of single-modality, static studies. This integration may enable a paradigm shift in liver cancer diagnosis and treatment, moving from morphological characterization to decoding of molecular behavior. Interdisciplinary collaboration and the development of an open-source ecosystem will be crucial to advancing the clinical implementation of intelligent imaging-based decision-making systems.

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Conflict of interest

The authors declare no competing interests.

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