



Reconstructing strategies for precision diagnosis and treatment of liver cancer based on multi-modal data

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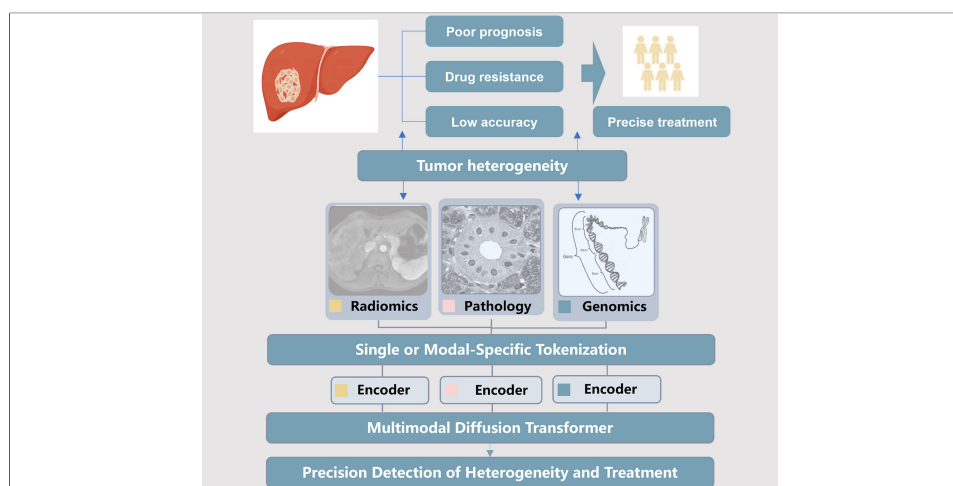
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Abstract

Liver cancer, particularly hepatocellular carcinoma (HCC), poses a severe global public health threat owing to its high incidence, frequent late-stage diagnosis, and poor 5-year survival rate. Conventional approaches to liver cancer diagnosis and treatment are limited by their reliance on subjective physician experience, uniform and undifferentiated treatment strategies, and imprecise prognostic assessment. This review synthesizes studies published between 2019 and 2025 on the application of multi-modal data in liver cancer care, including computed tomography (CT), magnetic resonance imaging (MRI), pathology, and multi-omics data. We explore the utility of single-modal data analysis including the role of CT or MRI in enhancing diagnostic accuracy and the application of pathological data. Subsequently, the review focuses on multi-modal data fusion strategies, including feature-level, decision-level, and modal-level fusion, which collectively support precision diagnosis, personalized treatment recommendation, and accurate prognosis prediction in clinical practice. Additionally, it addresses critical challenges such as data heterogeneity and low physician acceptance of integrated data-driven tools, while outlining

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future directions including the development of standardized multi-modal data ecosystems. This review highlights multi-modal data as a core driver of precision liver cancer care, with the objective of accelerating its translation into routine clinical practice.

INTRODUCTION

Liver cancer, as one of the most prevalent and lethal malignancies worldwide, poses an enormous threat to global public health. According to the latest global cancer statistics, it ranks as the sixth most diagnosed cancer and the third leading cause of cancer-related deaths, with an estimated 865,269 new cases and 757,948 deaths annually^[1]. Hepatocellular carcinoma (HCC), accounting for approximately 75%-85% of all liver cancer cases, is particularly prominent in regions such as East Asia and sub-Saharan Africa, where chronic hepatitis B virus (HBV) infection and alcohol exposure are highly prevalent^[2,3]. This review primarily focuses on HCC, which is the most clinically prevalent and well-studied subtype in the context of multi-modal data integration. For intrahepatic cholangiocarcinoma (ICC), combined Hepatocellular-Cholangiocarcinoma (HCC-CCA), and liver metastases, we briefly discuss their relevant multi-modal data applications where research evidence is available, while noting the current lack of large-scale multi-modal studies for these subtypes due to their relatively low incidence and heterogeneous pathological characteristics. Notably, in China alone, the incidence of liver cancer accounts for over 50% of the global total, and lots of patients are diagnosed at an advanced stage due to the lack of effective early screening strategies^[4,5]. This grim clinical reality underscores an urgent need to revolutionize the current paradigm of liver cancer diagnosis and treatment.

Traditional approaches to liver cancer management are plagued by inherent limitations that hinder the achievement of precision medicine. In the diagnostic phase, the identification of liver nodules and differentiation between benign and malignant lesions heavily rely on the subjective experience of radiologists and pathologists. For instance, the interpretation of imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) exhibits significant inter-observer variability, especially for small lesions which are often missed or misclassified^[6]. Pathological analysis, the gold standard for HCC diagnosis, is time-consuming, with microscopic evaluation of whole-slide imaging (WSI) taking up to 40 min per sample^[7]. In terms of treatment, a uniform and undifferentiated strategy, which includes transcatheter arterial chemoembolization (TACE), surgical resection, and targeted therapy, fails to account for tumor heterogeneity at the morphological, cellular, and molecular levels^[8,9]. This leads to suboptimal treatment responses, with nearly 50% of patients experiencing recurrence or metastasis with curative-intent treatment^[10,11]. Prognostic assessment, relying on single clinical indicators such as alpha-fetoprotein (AFP) and Tumor-Node-Metastasis (TNM) staging, also lacks sufficient accuracy to stratify patients into risk groups and guide personalized follow-up plans^[12,13].

In recent years, the rapid advancement of multi-modal data acquisition and artificial intelligence (AI) technology has opened new avenues for addressing these unmet needs in liver cancer care. Multi-modal data encompassing macroscopic tumor morphology, vascular status, pathological cellular features and multi-omics profiles integrates information from multiple sources that reflect tumor characteristics and provides a comprehensive perspective covering the macroscopic, microscopic and molecular dimensions of liver cancer, thus facilitating a more holistic understanding of tumor biology^[14,15]. AI, particularly deep learning and machine learning algorithms, excels at automated feature extraction, pattern recognition, and predictive modeling^[16-19]. For example, AI-driven imaging analysis can achieve a sensitivity of over 90% for liver nodule detection and identify patients as low risk with a high Negative Predictive Value (NPV) of 99.0%^[20-22]. AI-based pathological analysis is capable of classifying image patches as either HCC or

intrahepatic cholangiocarcinoma with an accuracy of 0.88, and AI-integrated analysis can reach an area under the curve (AUC) of 0.84 for early recurrence prediction^[23,24]. More importantly, the integration of multi-modal data via AI has emerged as a transformative approach for precision liver cancer diagnosis and treatment, enabling personalized clinical decision-making through accurate tumor characterization. AI-powered multi-modal fusion leverages complementary strengths across data types and overcomes limitations of individual modalities, thereby improving performance over single-modal approaches in key clinical tasks, including early diagnosis, treatment decision-making, and prognosis prediction^[25-27].

For this narrative review, we systematically searched peer-reviewed studies published between January 2019 and June 2025 in the PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI) databases. The key retrieval terms included combinations of “liver cancer/hepatocellular carcinoma”, “multimodal/multi-modal data”, “artificial intelligence/machine learning/deep learning”, “precision diagnosis/treatment”, “imaging/pathology/multi-omics”, and “data fusion”. We included original research articles, clinical trials, and systematic reviews that focused on the application of multi-modal data and AI in liver cancer diagnosis, prognosis, and treatment decision-making. We excluded non-English articles, conference abstracts, preprints without peer review. After screening titles, abstracts, and full texts, a total of 137 high-quality studies were finally included in this review for synthesis and analysis. This review aims to systematically synthesize the latest advances in multi-modal data analysis for liver cancer. It will first overview the applications of single-modal data as the foundation of precision care, then delve into the theoretical basis, technical strategies, and clinical applications of multi-modal fusion. Additionally, the current challenges in data quality, model interpretability, and clinical translation will be discussed, along with future directions to advance the integration of multi-modal into routine clinical practice. Ultimately, this review seeks to highlight the pivotal role of multi-modal in revolutionizing liver cancer care and improving patient outcomes.

SINGLE-MODAL DATA ANALYSIS IN LIVER CANCER: FOUNDATIONS FOR PRECISION

Single-modality data serves as the fundamental building block for understanding HCC biology and guiding clinical decisions. Unlike multi-modality data, which integrates information from multiple sources but may face challenges in data fusion and standardization, single-modality data offers the advantages of relatively straightforward acquisition, standardized protocols, and deep phenotypic characterization within a specific dimension. Imaging data primarily reflects the macroscopic structural and functional changes of the liver and tumors, providing critical information for tumor detection, localization, and staging^[28]. Pathological data reveals the microscopic cellular and histological features that determine tumor aggressiveness and treatment sensitivity^[29]. The application of AI to these data types enables the extraction of hidden, high-dimensional features that are imperceptible to the human eye, thereby enhancing the accuracy and efficiency of clinical assessments^[30] [Table 1].

Analysis of tumor macroscopic features from images

Imaging technology has long been an indispensable tool in the clinical workflow of HCC, from screening high-risk populations to monitoring treatment response^[31-33]. The integration of AI with various imaging modalities has revolutionized the analysis of tumor macroscopic features, enabling more precise clinical decision-making, including US, CT and MRI^[34].

US is the most widely used initial screening tool for HCC due to its non-invasiveness, portability, lack of ionizing radiation, and cost-effectiveness^[35,36]. However, the interpretation of US images is highly dependent on the operator's experience, leading to variability in diagnostic accuracy^[37,38]. AI has demonstrated significant potential in addressing these limitations, with key application directions including liver nodule detection, benign-malignant differentiation, and contrast-enhanced US (CEUS) analysis^[39,40].

Table 1. Single-modality AI applications in hepatocellular carcinoma

Modality	Main clinical tasks	Typical performance metrics	Key limitations	References
US/CEUS	Liver nodule detection; benign-malignant differentiation; CEUS phase analysis	Nodule detection: Sens = 90.2%, Spec = 78.0%; benign-malignant differentiation: AUC = 0.934; CEUS diagnosis: Acc = 85.0%	High operator dependence; low resolution for small lesions (< 1 cm); poor consistency in elastography parameter measurement	[41-43]
Contrast-enhanced CT	HCC segmentation; portal vein invasion detection; radiomic subtype classification	Tumor segmentation: DSC = 0.97; portal vein invasion: Sens = 87.0%, Spec = 66.0%	Poor soft tissue contrast for small HCC; vascular enhancement artifacts affect segmentation	[47-50]
DCE-MRI	Small HCC detection (≤ 3 cm); DCE-MRI TIC analysis; post-treatment recurrence prediction	Small HCC detection: Sens = 97.0%, Spec = 97.0%; TIC quantitative analysis: ICC = 0.92	High scan cost; long acquisition time; motion/breathing artifacts; limited availability in low-resource regions	[53,54]
Digital pathology/WSI	HCC/intrahepatic cholangiocarcinoma classification; MVI detection; tumor grading/staging; cancer cell identification	HCC/intrahepatic cholangiocarcinoma classification: Acc = 0.90; MVI detection: Acc = 94.25%	Time-consuming WSI scanning; subjective annotation standards; lack of 3D spatial tumor context	[64,68]
Genomics (ctDNA/tissue)	Driver gene mutation detection (TP53/CTNNB1); MRD monitoring; genetic risk prediction	Mutation detection: F1 = 0.91; recurrence risk: agreement = 80.0%	Low ctDNA allele frequency in early HCC; sequencing errors; inability to reflect spatial molecular heterogeneity; high test cost	[77,78,81,83]
Proteomics/Metabolomics	Serum biomarker panel development; Metabolic subtype classification; early HCC diagnosis; prognostic marker screening	4-protein panel diagnosis: AUC = 0.890, Sens = 0.909	Low specificity in chronic liver disease patients; serum protein degradation; large sample size requirement for panel validation	[87,88]

Sens: Sensitivity; Spec: specificity; Acc: accuracy; DSC: dice similarity coefficient; ICC: intraclass correlation coefficient; MRD: minimal residual disease; AUC: area under the curve; US: ultrasound; CEUS: contrast-enhanced ultrasound; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; TIC: time-intensity curve; WSI: whole-slide imaging; MVI: microvascular invasion; HCC: hepatocellular carcinoma.

In liver nodule detection, AI models, particularly deep learning-based object detection algorithms, have achieved remarkable performance. A study by Lu *et al.* developed an AI system for automatic detection of HCC nodules in US images, achieving a sensitivity of over 90% and a specificity of 78%, outperforming junior and intermediate radiologists. This high sensitivity is crucial for screening high-risk populations, as it minimizes the risk of missed diagnoses of early-stage tumors^[41]. For the differentiation of benign and malignant liver nodules, AI models can integrate multiple US features, including grayscale texture, blood flow characteristics, and elastography parameters, to establish a comprehensive classification model. Hu *et al.* proposed an AI model that combined conventional US and shear wave elastography data, achieving an AUC of 0.934 for distinguishing HCC from benign nodules, which was significantly higher than the accuracy of experienced radiologists^[42]. CEUS, which evaluates tumor vascularization by injecting contrast agents, provides additional functional information for HCC diagnosis. AI models can automatically segment the enhancement phases of CEUS and extract dynamic enhancement features to improve diagnostic accuracy. Ding *et al.* developed a temporal convolutional network for CEUS analysis, which accurately identified the characteristic “wash-in and wash-out” enhancement pattern of HCC, with an overall diagnostic accuracy of 85%^[43].

CT, especially contrast-enhanced CT, is a cornerstone imaging modality for HCC diagnosis and staging, offering high spatial resolution and clear visualization of tumor-vascular relationships^[44]. AI applications in CT imaging mainly focus on tumor segmentation, vascular invasion assessment, and subtype classification based on radiomics^[45,46].

Tumor segmentation is a prerequisite for quantitative analysis of tumor features, such as volume and growth rate. Traditional manual segmentation is time-consuming and subjective, while AI-based automatic segmentation models have shown superior efficiency and consistency. Özcan *et al.* developed a U-shaped Convolutional Network (U-Net)-based model for automatic segmentation of HCC in contrast-enhanced CT images, achieving a dice similarity coefficient (DSC) of 0.97^[47]. Vascular invasion is also a critical prognostic factor for HCC and directly influences treatment strategy selection^[48]. AI models can automatically identify and assess vascular invasion by analyzing the continuity and enhancement of blood vessels in CT images^[49]. A study by Xiao *et al.* applied a Convolutional Neural Network (CNN) to contrast-enhanced CT data, achieving a sensitivity of 87% and a specificity of 66% for detecting portal vein invasion, which was comparable to the performance of senior radiologists^[50].

MRI offers superior soft tissue contrast and multi-parametric imaging capabilities, making it the most sensitive modality for detecting small HCC and evaluating tumor function^[51]. With the advancement of deep learning, especially the application of Transformer architecture, AI has further expanded the clinical utility of MRI in HCC management. Early detection of small HCC is crucial for improving patient survival, as these tumors are often curable with surgical resection or ablation^[52]. However, small HCC nodules may have indistinct features on conventional MRI, leading to missed diagnoses^[6]. Zhong *et al.* proposed a Liver Imaging Reporting and Data System (LI-RADS) model for small HCC detection in T1 and T2-weighted MRI images, achieving a sensitivity of 97% and a specificity of 97%^[53]. Dynamic contrast-enhanced MRI (DCE-MRI), which evaluates the dynamic enhancement of tumors over time, provides important information about tumor angiogenesis and perfusion, making it a valuable tool for monitoring treatment efficacy. AI models can automatically analyze DCE-MRI time-intensity curves (TICs) to extract quantitative parameters, such as peak enhancement time and washout rate, which reflect changes in tumor vascularity after treatment^[54,55].

Analysis of tumor microscopic features in pathological examination

Pathological examination is the gold standard for HCC diagnosis, as it directly reveals the microscopic biological characteristics of tumors, which are critical for determining prognosis and guiding treatment^[56]. The advent of digital pathology, particularly WSI, has enabled the digitization of pathological slides, facilitating the application of AI for high-throughput and quantitative analysis of tumor microscopic features^[57]. WSI technology scans conventional glass slides at high resolution (up to 0.25 $\mu\text{m}/\text{pixel}$), generating digital images that can be viewed, analyzed, and shared electronically^[58]. WSI preserves the full histological context of the tissue sample, providing a rich dataset for AI analysis^[59-61]. The main AI tasks in digital pathology for HCC include cancer cell identification, tumor grading and staging, and microvascular invasion (MVI) detection, which has significant clinical translational value, particularly in improving diagnostic efficiency and guiding adjuvant treatment^[62].

AI models can automatically pre-screen slides, identify suspicious regions, and provide preliminary diagnostic suggestions, significantly reducing the workload of pathologists^[63]. Then, they can distinguish liver tumors and perform multi-class cancer classification with higher sensitivity and specificity^[64]. Guiding adjuvant treatment is another key clinical application. MVI status is a critical determinant of adjuvant treatment in HCC patients after surgical resection^[65]. Patients with MVI are at high risk of recurrence and may benefit from adjuvant therapies such as TACE, targeted therapy, or immunotherapy^[66,67]. AI-based MVI detection can provide accurate and timely information to guide treatment decisions. A prospective clinical trial conducted by Zhang *et al.* enrolled 753 HCC patients who had undergone surgical resection, based on which an AI-based diagnostic model for MVI was developed. This model demonstrated a high diagnostic accuracy of 94.25% in the independent external validation set. Notably, MVI-Artificial Intelligence Decision-Making Model (MVI-AIDM) can provide spatial information regarding MVI, a key piece of data that is critical for the accurate prediction of postoperative HCC recurrence^[68].

Analysis of tumor molecular features from multi-omics data

HCC exhibits profound molecular heterogeneity, which underlies its diverse clinical manifestations, treatment responses, and prognostic outcomes^[69,70]. Traditional single-marker approaches fail to capture the complex molecular landscape of HCC, limiting the precision of diagnosis and treatment. Multi-omics data, which integrates information from genomics, transcriptomics, proteomics, and metabolomics, provides a comprehensive view of tumor molecular characteristics^[71-73]. The integration of AI with multi-omics data enables the mining of hidden molecular patterns, offering unprecedented insights into HCC pathogenesis and personalized medicine^[74,75].

Genomic analysis, particularly of circulating tumor DNA (ctDNA) and tissue DNA, has emerged as a powerful tool for investigating the genetic basis of HCC^[76]. AI has significantly enhanced the utility of genomic data by enabling sensitive detection of mutations, accurate prediction of genetic risk, and reliable monitoring of minimal residual disease (MRD). One of the key applications of AI in HCC genomics is the detection of driver gene mutation, such as Tumor Protein 53 (TP53) and Catenin Beta 1 (CTNNB1), which are frequently mutated in HCC and play critical roles in tumor initiation and progression^[77,78]. Traditional sequencing analysis methods often face challenges in distinguishing true mutations from sequencing errors, especially in low-allele-frequency ctDNA samples. AI models, such as deep learning-based variant callers, can integrate multiple sequencing features to improve mutation detection accuracy^[79]. Genetic risk prediction is another important application of AI in HCC genomics. By integrating genomic data with clinical and environmental factors, AI models can identify individuals at high risk of HCC development or recurrence, facilitating early screening and intervention^[80]. Shen *et al.* constructed a machine learning model that used seven genetic variants to predict HCC recurrence risk. The agreement rate between the results from the decision tree model and the clinical observation reached 80%. This risk prediction model can help prioritize high-risk individuals for intensive screening, reducing the burden of population-wide screening^[81].

MRD monitoring, which detects residual tumor cells after curative treatment, is crucial for predicting recurrence and guiding adjuvant therapy^[82]. AI models can analyze ctDNA dynamics to identify MRD and predict recurrence risk. Huang *et al.* found that serial blood samples collected for profiling ctDNA mutations can predict tumor recurrence after liver transplantation^[83]. Baseline ctDNA mutational profiles were compared with those of matched tumor tissues. This early detection of MRD enables timely intervention, potentially improving patient survival. In addition to mutation detection and risk prediction, AI can also assist in molecular subtype classification and prognostic gene marker screening^[84]. Chen *et al.* applied a computational framework to integrate multi-omics data from HCC patients using the latest ten different clustering algorithms. They distinguished two subtypes of liver cancer and found that patients with subtype 2 exhibited superior overall survival (OS). AI-based subtype classification can provide valuable information for tailoring treatment strategies, such as using targeted therapy for the proliferative subtype and metabolic modulators for the metabolic subtype^[85].

Proteomics and metabolomics provide complementary information to genomics, reflecting the functional state of tumors at the protein and metabolite levels^[86]. AI models can integrate proteomic and metabolomic data to identify biomarkers for early diagnosis and survival prediction^[87]. Xing *et al.* conducted a large-scale proteomic study of serum samples from 1,000 HCC patients. They identified a 4-protein panel for HCC and healthy person diagnosis. This panel achieved an AUC of 0.890 and a sensitivity of 0.909. The 4-protein panel was particularly effective in distinguishing patients with liver cancer and healthy persons^[88].

Table 2. Multi-modal data fusion for hepatocellular carcinoma

Modality combinations	Fusion strategy	Clinical endpoint	Validation type	Interpretability method used	References
Digital histopathology (WSI) + Genomics (MSI molecular detection)	Feature-level fusion	MSI status prediction in cancer via histology; non-invasive surrogate for molecular MSI detection	Multi-center external validation	Histopathological feature heatmap visualization; deep learning attention region mapping; MSI-associated morphological feature mining	[99]
Contrast-enhanced CT/MRI Radiomics + Clinical covariates (cirrhosis background)	Feature-level fusion	HCC diagnosis; HCC recurrence prediction after surgical resection; radiomics machine-learning signature construction and validation	External multi-center	Radiomic feature selection and ranking; machine-learning signature weight visualization; diagnostic performance subgroup analysis (cirrhosis subtype)	[101-103]
Multi-parametric imaging (CT/MRI) + Transcriptomics (transcriptome subclasses/signatures)	Modal-level fusion	HCC transcriptome subclass non-invasive prediction; imaging surrogate marker identification for transcriptome signatures; tumor biological behavior correlation analysis	Internal + external validation	Imaging feature-transcriptome signature correlation analysis; subtype-specific imaging phenotype visualization; radiomic signature enrichment analysis	[105]
Digital pathology/WSI + clinical data + ctDNA	Multi-level fusion (feature+decision)	Postoperative recurrence prediction; adjuvant therapy guidance (TACE/lenvatinib)	Prospective multi-center	Grad-CAM (WSI); SHAP values (clinical/omics)	[107,108]
CT radiomics + Genomics (ADH1A gene/retinol metabolism pathway)	Feature-level fusion	HCC OS prediction; retinol metabolism pathway-related molecular feature correlation analysis	External multi-center	Radiomic feature ranking; pathway enrichment analysis; ADH1A expression-radiomic feature correlation plot	[109]

HCC: Hepatocellular carcinoma; MVI: microvascular invasion; CT: computed tomography; MRI: magnetic resonance imaging; WSI: whole-slide imaging; ctDNA: circulating tumor DNA; TACE: transcatheter arterial chemoembolization; CEUS: contrast-enhanced ultrasound; US: ultrasound; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; TIC: time-intensity curve; OS: overall survival; SHAP: SHapley Additive exPlanations.

MULTI-MODAL DATA FUSION FOR PRECISION IN LIVER CANCER DIAGNOSIS AND TREATMENT

While single-modality data has laid a solid foundation for HCC precision medicine, each modality inherently has limitations. Images capture macroscopic structure but lack molecular insights; pathology reveals microscopic features yet lacks spatial context of the entire tumor, and multi-omics deciphers molecular heterogeneity but cannot reflect morphological characteristics^[89-91]. AI-powered multi-modal fusion, which integrates complementary information from multiple modalities, has emerged as a transformative approach to overcome these limitations and achieve a more comprehensive understanding of HCC. This section elaborates on the theoretical basis, technical strategies, and clinical applications of multi-modal fusion [Table 2].

The theoretical foundation of multi-modal fusion lies in the complementarity of cross-dimensional information and the integrity of tumor phenotypic characterization^[92-94]. Tumor development is a complex process involving the interaction of macroscopic structure, microscopic morphology, and molecular regulation^[78,95]. No single modality can fully capture the multi-level characteristics of tumors, and the limitations of individual modalities often restrict the accuracy of clinical assessments^[96,97]. Multi-modal fusion addresses these limitations by integrating information from different modalities to construct a comprehensive model that encompasses the macro, micro, and molecular scale dimensions. This integrated model achieves three core objectives to advance medical research and clinical practice. First, it mitigates single-modality information limitations by fusing imaging spatial data with omics molecular data, enabling

accurate identification of region-specific molecular alterations^[98]. Second, it reduces uncertainty in clinical assessments via cross-validating multi-modal conclusions, significantly enhancing result reliability and reproducibility^[92]. Third, it facilitates discovery of novel cross-modal associations providing new insights into tumor biology^[99]. Collectively, this model serves as a robust tool to support personalized diagnosis, evidence-based treatment decision-making and precision prognosis prediction, bridging the gap between multi-omics research and clinical utility in precision oncology.

In HCC research and clinical practice, the radio-genomics approach has made substantial progress in establishing associations between specific imaging traits and underlying molecular characteristics^[100,101]. It correlates contrast-enhanced CT/MRI features including arterial hyperenhancement, washout, and irregular tumor margins with angiogenic pathway activation, cellular proliferation, and aggressive tumor behavior. For example, a non-invasive radiological signature linked to the “proliferation class” of HCC enables identification of patients at high risk of early recurrence^[102]. Radiomic models also show utility in predicting mutations in key genes such as CTNNB1, which correlate with less aggressive tumor phenotypes and hypo-vascular imaging appearances^[103]. Notably, this radio-genomic approach overcomes the spatial limitations of traditional biopsy by enabling non-invasive mapping of molecular alterations across the entire tumor volume, a capability critical for guiding targeted therapy selection and predicting disease progression^[104,105].

The ultimate value of multi-modal data fusion lies in the development of clinical decision support systems that generate actionable clinical recommendations for diagnosis, treatment selection, and prognosis prediction^[99]. For patients with newly diagnosed HCC, such systems can synthesize multi-dimensional data including clinical variables, radiological phenotypes, AI-derived pathological scores, and circulating biomarkers to construct a comprehensive composite risk profile^[106].

Clinical variables include age and liver function, radiological phenotypes come from CT/MRI, AI-derived pathological scores are from biopsy whole-slide images, and circulating biomarkers include AFP and ctDNA. This profile not only predicts OS but also forecasts response to specific interventions such as lenvatinib, immune checkpoint inhibitors, or transarterial chemoembolization^[107-109]. Additionally, multi-modal clinical decision support systems reduce diagnostic and prognostic uncertainty through cross-validation of findings across data types^[110,111]. This process boosts the reliability and reproducibility of clinical assessments.

Collectively, multi-modal data fusion is reshaping the landscape of HCC management by translating the abstract concept of precision oncology into tangible clinical tools. By integrating macroscopic, microscopic, and molecular information, this approach transcends the limitations of one-dimensional assessments, enabling a comprehensive understanding of each patient’s unique tumor biology and driving more personalized, effective HCC care. Macroscopic information refers to radiological data, microscopic information refers to pathological data, and molecular information includes genomic data and biomarker data.

CURRENT CHALLENGES IN MULTI-MODAL LIVER CANCER CARE

Despite the significant progress made in integrating AI with single-modality data for HCC precision diagnosis and treatment, several challenges remain to be addressed for broader clinical implementation^[112].

One of the major challenges is the lack of standardized and high-quality datasets. AI models require large-scale, well-annotated datasets for training and validation; however, current datasets often suffer from heterogeneity in data acquisition protocols, annotation standards, and patient populations^[113,114]. For example, imaging data may vary across different scanners and institutions, while pathological data may have

different staining protocols and annotation criteria. This heterogeneity can reduce the generalizability of AI models. To address this issue, international consortia and research institutions should collaborate to establish standardized data acquisition and annotation protocols, and share large-scale multi-center datasets such as Global Alliance for Genomics and Health (GA4GH)^[115]. The development of federated learning (FL), which enables model training across multiple institutions without sharing raw data, can also help overcome data privacy and accessibility issues^[116].

Another challenge is the interpretability of AI models. Most state-of-the-art AI models, such as deep learning models, are “black boxes” that make predictions without providing clear explanations of the underlying reasoning^[117,118]. This lack of interpretability limits clinical trust and acceptance, as clinicians need to understand how AI models arrive at their conclusions to make informed decisions. To improve model interpretability, researchers are developing explainable AI (XAI) techniques, such as attention mechanisms and gradient-weighted class activation mapping (Grad-CAM), which can visualize the regions of the image or features that the model uses for prediction^[119,120]. For example, Grad-CAM can highlight the tumor regions in imaging data that the AI model uses for diagnosis, providing a visual explanation for clinicians^[121]. Integrating XAI into clinical AI systems will be crucial for their widespread adoption.

The clinical validation and regulatory approval of AI models are also significant challenges. Most AI models are currently developed and validated in retrospective studies, and their performance in prospective clinical trials remains to be demonstrated^[122,123]. Beyond data heterogeneity and poor model interpretability, multi-modal AI studies targeting liver cancer are confronted with several typical failure modes that severely impede their clinical translation and practical application. First and foremost, dataset shift is prevalent due to variations in imaging scanners, pathological staining protocols, and multi-omics sequencing platforms among different institutions, which significantly compromises the generalizability of models trained on single-center datasets. Secondly, data leakage, characterized by improper partitioning of training and validation sets and the inclusion of post-diagnosis variables in prognostic models, often results in overestimated model performance and misleading evaluations. Thirdly, the absence of standardized gold standards for clinical endpoints undermines the reliability of model training and validation processes, thereby affecting the credibility of research findings. Finally, most current multi-modal models lack robust strategies for addressing missing data, which may lead to model breakdown or biased predictions when applied in real-world clinical scenarios.

FUTURE DIRECTIONS: ADVANCING PRECISION AND CLINICAL IMPACT

Advancing the accuracy and clinical utility of HCC management requires continuous innovation and breakthroughs across multiple technological domains. Recent progress in AI is profoundly transforming this field through several key technological advancements.

XAI facilitates precision diagnosis and treatment of cancer by incorporating attention mechanisms and visualization tools, aiding in the identification of biomarkers and the development of robust predictive models for early detection^[124]. The integration of XAI with machine learning improves diagnostic accuracy and aligns with the overarching objectives of precision medicine^[125]. FL offers a privacy-enhancing approach by integrating 2D and 3D deep learning models within an FL framework to achieve accurate segmentation of liver and tumor regions in medical images^[126]. The FL framework demonstrates considerable potential for improving tumor detection accuracy, indicating strong suitability for integration into clinical and hospital environments.

Medical digital twins represent an emerging paradigm in personalized medicine, structured around five core elements: patients, data connectivity, in-silico patient models, interactive interfaces, and twin synchronization^[127,128]. By integrating multi-modal data and leveraging AI, they enable personalized clinical

decision-making, disease progression prediction, and treatment simulation, thereby enhancing both the precision and efficiency of healthcare delivery. Optimization of the data ecosystem, particularly through database standardization, is crucial for supporting AI-driven healthcare innovations^[129,130]. Multi-modal data, when combined with deep learning techniques, significantly enhances the diagnosis and prediction of HCC. The integration of diverse data sources, such as blood tests, CT, MRI, and biopsy samples, improves diagnostic accuracy over single-modality approaches and contributes to the construction of more reliable risk stratification models^[131]. Furthermore, multi-modal AI technology enhances the extraction of clinically relevant features and supports more accurate predictive analytics^[132,133]. The application of AI in medicine has been extensively explored. Recent advances in deep learning have substantially improved the analysis of medical images, particularly by extracting diagnostic, prognostic, and predictive information from radiological imaging data^[134,135]. To address these evidence quality issues and standardize multi-modal AI research in liver cancer, adherence to specialized reporting and validation frameworks, including TRIPOD-AI, CONSORT-AI, and SPIRIT-AI, is critical. These frameworks guide researchers to standardize study design, data processing, model validation, and result reporting, thereby improving the transparency and reproducibility of research. For future clinical translation, external multi-center validation and prospective clinical impact studies are the core next steps. External validation verifies the generalizability of models in real-world heterogeneous datasets, while prospective studies directly evaluate whether the application of multi-modal AI tools improves clinical outcomes rather than just technical performance metrics.

However, significant challenges remain in translating algorithmic advancements into clinical practice. Many AI models exhibit high accuracy in controlled research settings but are seldom implemented in real-world clinical scenarios^[136,137]. Future research should prioritize the development of clinically actionable models that integrate seamlessly into existing healthcare workflows, which involves adapting models to meet clinical requirements and ensuring they are accessible and user-friendly for healthcare professionals.

CONCLUSION

Liver cancer remains a major global health challenge, and traditional clinical care has long fallen short of meeting the demands of precision medicine. This shortfall stems from reliance on subjective diagnostic assessments, uniform treatment strategies that fail to account for individual variability, and imprecise prognostic evaluations. Synthesizing recent evidence, this review confirms that multi-modal data integration, empowered by AI, stands as a transformative solution to address these critical gaps. Single-modal data serves as a solid foundation for this advancement, and AI-enhanced imaging improves the detection of small lesions that may otherwise be overlooked. AI-accelerated pathological analysis streamlines diagnostic workflows, and multi-omics data uncovers the molecular heterogeneity of tumors. More importantly, multi-modal data fusion generates synergies that outperform single-modal tools alone. It reduces variability in diagnostic interpretations, enables the design of personalized treatment plans tailored to individual patient needs, and refines prognostic assessments, which firmly establishes multi-modal data as a core driver of precision liver cancer care.

However, translating these advances into routine clinical practice requires overcoming several key barriers. These include data heterogeneity across collection and analysis platforms, the opacity of some AI systems (often referred to as “black-box” models), limited evidence from large-scale prospective clinical trials, data privacy concerns, and resource shortages in low-resource regions that restrict equitable access. Future efforts must prioritize the development of standardized multi-modal data ecosystems, the advancement of XAI to enhance clinical trust, and the execution of prospective multi-center trials to validate tool performance. Equally critical is fostering interdisciplinary collaboration across clinical specialties and data science, alongside initiatives to expand equitable access.

In conclusion, multi-modal data holds great promise for revolutionizing liver cancer care. Resolving current challenges will accelerate its translation into clinical practice, ultimately reducing the global burden of this devastating disease and improving outcomes for patients worldwide.

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Availability of data and materials

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AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (OpenAI, San Francisco, USA) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

Yang XR is an Associate Chief Editor of the journal *Hepatoma Research* and also served as a Guest Editor for the Special Issue *Advancing Multimodal Approaches in Liver Cancer: From Tumor Heterogeneity to Precision Therapies*. Yang XR was not involved in any part of the editorial process, including reviewer selection, manuscript handling, or decision-making. The other authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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