
Hepatic Nodule Monitoring in Hepatitis B Related Cirrhosis: A Survey

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Abstract

This survey explores hepatic nodule monitoring within Hepatitis B-related cirrhosis, emphasizing the prevention of hepatocellular carcinoma (HCC) through advanced imaging and comprehensive management strategies. Hepatitis B-related cirrhosis serves as a precursor to HCC, necessitating vigilant surveillance to enable early intervention and improve patient outcomes. Traditional imaging techniques like ultrasound, CT, and MRI are foundational, but advanced modalities such as contrast-enhanced ultrasound (CEUS) and MRI offer enhanced diagnostic precision. The integration of artificial intelligence and machine learning further refines imaging analysis, facilitating timely diagnosis and intervention. The survey highlights the significance of antiviral therapies, particularly tenofovir disoproxil fumarate (TDF), in reducing HCC risk, alongside lifestyle modifications and vaccination as preventive measures. Challenges in monitoring cirrhosis progression include the asymptomatic nature of early disease, variability in imaging techniques, and the need for reliable biomarkers. The survey underscores the importance of multi-disciplinary approaches and personalized treatment plans, integrating molecular profiling and risk stratification to optimize management strategies. Future research should focus on understanding the genetic and epigenetic factors influencing liver carcinogenesis, developing non-invasive diagnostic tools, and exploring novel therapeutic targets. By advancing diagnostic techniques and preventive strategies, the burden of Hepatitis B-related cirrhosis and HCC can be significantly reduced, enhancing patient care and survival outcomes.

1 Introduction

1.1 Significance of Hepatic Nodule Monitoring

Monitoring hepatic nodules in patients with Hepatitis B-related cirrhosis is crucial for the early detection and prevention of hepatocellular carcinoma (HCC), which ranks as the sixth most common cancer and the third leading cause of cancer-related mortality worldwide [1]. The increasing incidence of HCC, particularly linked to chronic Hepatitis B virus (HBV) infection, necessitates effective surveillance strategies to identify oncogenic factors and mechanisms involved in HCC development [2]. Early detection is vital, as it significantly improves treatment outcomes and reduces mortality rates [3].

Current surveillance methods, such as biannual ultrasound, exhibit limitations in sensitivity and application rates, often leading to late HCC diagnoses [4]. These limitations are notably significant in detecting hypovascular nodules during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI [1]. Thus, there is an urgent need for enhanced surveillance protocols that can be effectively integrated into clinical practice to monitor cirrhosis progression and mitigate HCC risk [5].

Integrating surveillance into routine clinical practice is essential, as it aids in the early identification of malignant transformations in hepatic nodules and supports the development of individualized treatment plans critical for optimizing patient outcomes [6]. Comprehensive clinical management

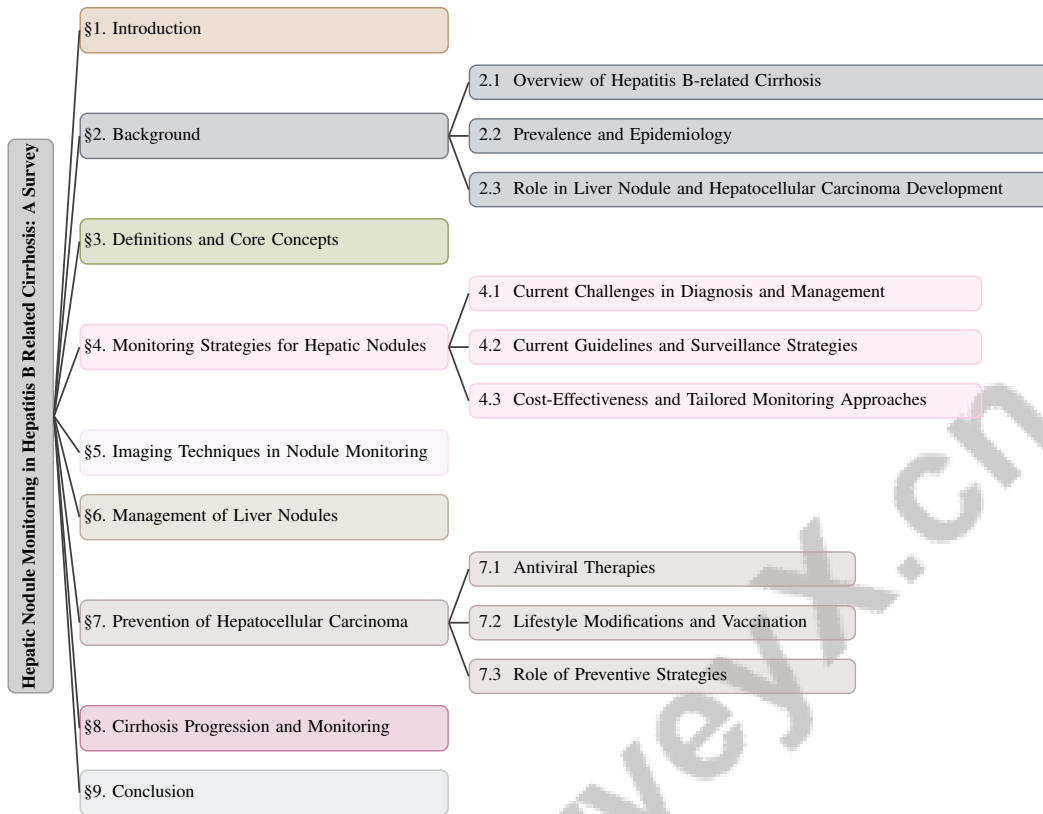


Figure 1: chapter structure

guidelines that address knowledge gaps and provide updated information are necessary to elevate the standard of care for patients with liver cirrhosis and HCC [7]. These guidelines are informed by literature reviews and expert consensus, aiming to enhance clinical practices in liver cirrhosis management [8].

1.2 Structure of the Survey

This survey provides a thorough examination of hepatic nodule monitoring within the context of Hepatitis B-related cirrhosis, a critical area for HCC prevention and cirrhosis management. The introduction highlights the significance of hepatic nodule monitoring in early HCC detection and prevention. The background section offers an overview of Hepatitis B-related cirrhosis, discussing its pathophysiology, prevalence, and contribution to liver nodule formation and HCC development.

Key terms and concepts are defined in the third section to establish a foundation for understanding the monitoring strategies discussed later, including genetic and epigenetic factors influencing cirrhosis and HCC. The subsequent section addresses various monitoring strategies for hepatic nodules, focusing on current challenges, guidelines, and cost-effectiveness.

The fifth section reviews imaging techniques used in nodule monitoring, discussing both traditional methods and recent advancements, including the role of artificial intelligence and machine learning in improving diagnostic accuracy. Management of liver nodules is detailed next, emphasizing individualized treatment plans, decision-making frameworks, and complication management.

Prevention strategies for HCC in patients with Hepatitis B-related cirrhosis are examined in the seventh section, underscoring the importance of antiviral therapies, lifestyle modifications, and vaccination. The penultimate section discusses cirrhosis progression and monitoring, including the integration of biomarkers and molecular data, as well as risk stratification methods.

The survey concludes by synthesizing critical findings related to hepatic nodule monitoring in patients with Hepatitis B-related cirrhosis, highlighting significant alterations in gut microbiota associated

with disease progression, the evolving role of liver biopsy in HCC diagnosis, and the need for innovative screening and management strategies for cirrhosis. It also outlines prospective research avenues aimed at enhancing our understanding of these interrelated factors, providing a detailed roadmap for advancing clinical practices in this complex medical landscape [9, 10, 11]. The following sections are organized as shown in Figure 1.

2 Background

2.1 Overview of Hepatitis B-related Cirrhosis

Hepatitis B-related cirrhosis poses a significant clinical challenge due to its prevalence and its progression to hepatocellular carcinoma (HCC), a leading cause of cancer mortality. Chronic Hepatitis B virus (HBV) infection remains a primary contributor to chronic liver diseases, including cirrhosis and HCC [8]. The pathophysiology involves complex interactions between HBV replication and host immune responses, leading to sustained liver inflammation and fibrosis [12]. This inflammatory milieu, maintained by immune cells such as Kupffer cells, monocytes, and macrophages, results in fibrosis and impaired liver function [13, 8].

Diagnosing and managing HBV-related cirrhosis is challenging, with liver biopsy being crucial for accurate HCC diagnosis, especially in early stages where detection is difficult [8]. The disease's complexity is particularly evident in high-prevalence regions like East Asia, complicating management [14, 15]. Historical links between HBV and HCV infections and HCC emphasize the need for preventive strategies to mitigate disease progression [12].

2.2 Prevalence and Epidemiology

Globally, HBV infection and its progression to cirrhosis and HCC present substantial health challenges, significantly impacting morbidity and mortality rates [16]. The highest prevalence is in Asia and sub-Saharan Africa, where chronic HBV infection is endemic, contributing to elevated incidences of cirrhosis and HCC [17]. In the United States, approximately 2.2 million adults are affected by cirrhosis, necessitating effective management strategies [18]. The epidemiology is complex, with various etiologies such as viral hepatitis, alcohol consumption, and non-alcoholic fatty liver disease contributing to the disease burden [17]. Complications like portal hypertension and hepatic encephalopathy further exacerbate this burden [17].

Rising HCC incidence and mortality highlight the global impact of chronic HBV and HCV infections on liver carcinogenesis [16]. Genetic and epigenetic factors associated with these infections are crucial for understanding cirrhosis progression to HCC [19]. Addressing HBV-related cirrhosis epidemiology requires a multifaceted approach, including surveillance, early diagnosis, and tailored therapies to reduce HCC progression and improve outcomes. Sustained research and comprehensive policy initiatives are essential to mitigate the public health impact, focusing on early detection, improved treatment, and addressing risk factors [20, 10, 16, 21].

2.3 Role in Liver Nodule and Hepatocellular Carcinoma Development

The progression from liver nodules to HCC in HBV-related cirrhosis involves a complex interplay of viral, host, and environmental factors. Chronic HBV infection induces persistent liver inflammation and fibrosis, precursors to dysplastic nodules that may evolve into HCC [2]. This inflammatory environment promotes hepatocarcinogenesis through cellular proliferation and genomic instability [12]. HCC frequently develops from cirrhosis due to chronic HBV infection, presenting management challenges and underscoring the need for early diagnosis [22, 8]. The absence of consensus on intermediate-stage HCC treatment, especially with new therapies potentially outperforming transarterial chemoembolization (TACE), necessitates optimized strategies [23].

HCC's rapid progression and recurrence post-treatment demand tailored management strategies [7]. The gut microbiota's role in HBV-related liver disease progression, with specific bacterial taxa linked to infection stages, highlights the importance of integrating viral and host factors in surveillance and management [24]. Routine imaging surveillance, as recommended by the American Association for the Study of Liver Disease, is critical for early HCC detection. However, low sensitivity of current

imaging methods, particularly ultrasonography, complicates monitoring, necessitating advanced modalities for accurate diagnosis and risk stratification [1].

In recent years, the understanding of Hepatitis B-related cirrhosis and its progression to hepatocellular carcinoma (HCC) has evolved significantly. This evolution is largely due to advancements in imaging techniques and the identification of genetic and epigenetic alterations that play crucial roles in the disease's diagnosis and management. To elucidate these complex relationships, Figure ?? illustrates the hierarchical structure of concepts related to this progression. The figure categorizes key definitions, imaging modalities, genetic alterations, and epigenetic modifications, thereby emphasizing their integral roles in diagnosis, monitoring, and treatment strategies. This comprehensive framework not only aids in visualizing the intricate interplay of these elements but also enhances our understanding of their implications in clinical practice.

Figure 2: This figure illustrates the hierarchical structure of concepts related to Hepatitis B-related cirrhosis and its progression to hepatocellular carcinoma (HCC). It categorizes key definitions, imaging techniques, genetic alterations, and epigenetic modifications, emphasizing their roles in diagnosis, monitoring, and treatment strategies.

3 Definitions and Core Concepts

3.1 Key Definitions

Understanding key terms is crucial in managing Hepatitis B-related cirrhosis and its progression to hepatocellular carcinoma (HCC). Hepatic nodules, varying from benign to malignant, are focal liver lesions whose vascularity and growth patterns are essential for risk assessment. Hypovascular nodules may progress to hypervascular HCC, as shown by gadolinium-enhanced MRI studies. Identifying size thresholds linked to progression risk is vital, and liver biopsy remains crucial when imaging is inconclusive, providing histopathological insights for treatment and prognosis [1, 25, 11]. These nodules often arise in chronic liver disease and cirrhosis, driven by inflammation and fibrosis.

Cirrhosis, marked by scar tissue replacing healthy liver tissue, impairs liver function and is commonly linked with chronic Hepatitis B virus (HBV) infection, significantly heightening HCC risk. Most HCC cases occur in cirrhotic patients, necessitating regular monitoring through surveillance programs like abdominal ultrasound for early malignant detection, thus improving prognosis and access to curative therapies [5, 25, 11, 19]. HCC, which constitutes 75

Imaging techniques are pivotal for the surveillance and diagnosis of hepatic nodules and HCC. Traditional modalities like ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are routinely used, while advanced techniques such as contrast-enhanced ultrasound and multiparametric MRI enhance sensitivity and specificity for detecting liver lesions. New metrics, including SSEGEP, which emphasizes smaller segment pixels, aim to improve diagnostic accuracy beyond existing metrics like Dice and IOU [26].

A thorough grasp of liver nodule definitions is essential for clinicians and researchers managing Hepatitis B-related cirrhosis, enabling accurate monitoring and timely interventions. This knowledge is critical for preventing progression to HCC, a common and lethal cancer associated with cirrhosis, ultimately improving patient outcomes. Advancements in imaging and molecular analysis further enhance the ability to tailor surveillance strategies and therapeutic approaches to individual patient needs [11, 12, 25, 19, 6].

3.2 Genetic and Epigenetic Factors

The progression from liver cirrhosis to hepatocellular carcinoma (HCC) in Hepatitis B-related liver disease is significantly influenced by genetic and epigenetic factors, crucial for understanding HCC pathogenesis and offering potential therapeutic targets and prognostic markers. Genetic alterations, including mutations in oncogenes and tumor suppressor genes, play a pivotal role in the malignant transformation of hepatic nodules [12].

As illustrated in Figure 3, which categorizes the key genetic and epigenetic factors influencing this progression, these factors are divided into three main categories: genetic alterations, epigenetic

modifications, and viral contributions. This figure underscores the significant roles each category plays in the pathogenesis of HCC.

Epigenetic modifications such as DNA methylation, histone modification, and non-coding RNA regulation further complicate liver carcinogenesis. MicroRNAs (miRNAs) have emerged as key regulators of gene expression, affecting cellular processes like proliferation, apoptosis, and differentiation. Dysregulation of miRNAs is implicated in the progression from liver cirrhosis to HCC, highlighting their potential as biomarkers for early detection and therapeutic targets [19].

Additionally, viral proteins encoded by the Hepatitis B virus (HBV) contribute to hepatocarcinogenesis by interacting with host cellular machinery, leading to genomic instability and oncogenic pathway activation. The integration of HBV DNA into the host genome can induce chromosomal rearrangements and activate proto-oncogenes, facilitating HCC development [12].

Current research frameworks emphasize the complex interactions among genetic mutations, epigenetic modifications, and viral factors—particularly those associated with HBV and HCV—in the progression from liver cirrhosis to HCC, which is notably prevalent among affected patients [20, 12, 19]. Understanding these interactions enables the development of more effective monitoring strategies and personalized treatment approaches for patients with Hepatitis B-related liver disease.

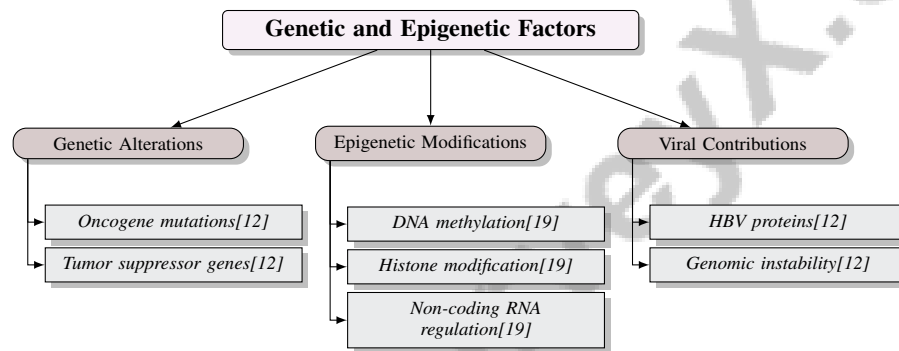


Figure 3: This figure illustrates the key genetic and epigenetic factors influencing the progression from liver cirrhosis to hepatocellular carcinoma (HCC) in Hepatitis B-related liver disease. It categorizes these factors into genetic alterations, epigenetic modifications, and viral contributions, highlighting significant roles in HCC pathogenesis.

4 Monitoring Strategies for Hepatic Nodules

The management of hepatic nodules in Hepatitis B-related cirrhosis involves complex diagnostic and therapeutic challenges, influenced by factors such as viral infections, alcohol use, and metabolic disorders. Identifying high-risk individuals, implementing effective surveillance, and managing cirrhosis complications are crucial for early HCC diagnosis and improved patient outcomes. Current guidelines stress understanding these risk factors alongside regional disease variations to tailor clinical approaches for HCC management [10, 6]. Addressing these challenges requires a comprehensive grasp of diagnostic hurdles and management intricacies, providing a foundation for exploring existing guidelines and surveillance strategies.

4.1 Current Challenges in Diagnosis and Management

Diagnosing and managing liver nodules in Hepatitis B-related cirrhosis is complicated by factors impacting clinical outcomes. Early liver cirrhosis is often asymptomatic, leading to late-stage detection [12]. Public unawareness and misunderstanding of cirrhosis further hinder early intervention [17]. Current diagnostic methods often lack the sensitivity and specificity to distinguish HCC from cirrhosis reliably, complicating clinical decisions [22]. Variability in ultrasound image quality due to differing examination conditions challenges accurate liver tumor diagnosis [27], and traditional metrics often neglect smaller segments crucial for early disease detection [26].

The increasing incidence of cirrhosis, driven by alcohol consumption and NAFLD, adds to the liver disease burden [17]. Genetic and epigenetic factors further complicate understanding HCC

progression, challenging the development of effective monitoring strategies [12]. Research is limited by a lack of comprehensive insights into HBV oncogenesis, partly due to the absence of effective animal models [2]. Management is also complicated by the arbitrary allocation of MELD exception points and the limitations of the MELD scoring system, which may not adequately represent all patients [28]. Uncertainty about the malignant potential of hepatic tumors like PEComas adds complexity to management decisions [29].

Despite treatment advancements, HCC patient outcomes remain unsatisfactory, highlighting the need for refined guidelines and individualized treatment plans considering patient characteristics and treatment responses. Addressing the rising HCC incidence requires a comprehensive strategy, including advancements in diagnostic tools, such as AI integration in imaging techniques to enhance liver tumor identification accuracy, and promoting public awareness about risk factors, especially in high-prevalence regions. Developing personalized management strategies informed by histopathological insights and molecular classifications is crucial for optimizing patient outcomes [30, 25, 21, 27].

4.2 Current Guidelines and Surveillance Strategies

Surveillance of hepatic nodules in Hepatitis B-related cirrhosis is supported by frameworks integrating diagnostic, preventive, and therapeutic strategies for effective HCC management. These guidelines reflect diverse regional approaches, emphasizing tailored surveillance methods and diagnostic criteria, including size-based and non-size-based pathways [7]. Advanced imaging modalities, such as MRI and CEUS, enhance early hepatic nodule detection, with CEUS providing real-time assessments of tumor perfusion and vascular changes [31, 32]. Novel frameworks for categorizing hepatic PEComas based on CEUS imaging characteristics highlight advancements in surveillance protocols [29].

Guidelines also highlight the importance of molecular classifications and histopathological analyses in understanding tumor characteristics and informing treatment decisions, integral to stratifying patients into appropriate treatment pathways and facilitating personalized surveillance strategies [22]. The use of non-targeted metabolomics and targeted eicosanoid analysis to identify serum markers distinguishing HCC from HBV-cirrhosis exemplifies the integration of molecular data into clinical practice [22].

The development of new evaluation metrics, such as SSEGEP, emphasizing the detection of smaller segments in medical images, enhances diagnostic accuracy and facilitates better segmentation algorithm comparisons [26]. This advancement is crucial for improving imaging technique sensitivity in detecting early-stage nodules, enabling timely intervention.

4.3 Cost-Effectiveness and Tailored Monitoring Approaches

Benchmark	Size	Domain	Task Format	Metric
LI-RADS-CEUS[33]	56	Hepatology	Diagnostic Classification	Diagnostic accuracy, Inter-observer agreement
PENLACC:ES[9]	97	Microbiology	Microbial Community Analysis	AUC
SSEGEP[26]	379	Medical Image Segmentation	Segmentation	SSEGEP, DSC
HCC-Nodules[1]	91	Hepatology	Nodule Progression Analysis	AUROC, sensitivity

Table 1: This table presents a selection of representative benchmarks relevant to the evaluation of monitoring strategies in various medical domains, including hepatology and microbiology. It details the benchmark names, their respective sizes, domains, task formats, and the metrics used for performance evaluation, highlighting the diversity and scope of current research efforts.

Evaluating the cost-effectiveness of monitoring strategies for hepatic nodules in Hepatitis B-related cirrhosis is essential for optimizing healthcare resource allocation and improving patient outcomes. The rising incidence of cirrhosis, particularly from alcohol and NAFLD, underscores the need for efficient monitoring approaches [17]. Current research identifies therapies managing cirrhosis symptoms and complications, enhancing patient quality of life and survival rates [18]. However, the economic burden of cirrhosis-related healthcare necessitates cost-effective surveillance strategies. Table 1 provides an overview of representative benchmarks utilized in the evaluation of cost-effective and tailored monitoring approaches for hepatic nodules and other medical applications.

Advanced imaging techniques, such as CEUS and MRI, offer improved sensitivity in detecting hepatic nodules, but their high costs challenge widespread implementation [31]. Model-based quantitative ultrasound (MB-QRUS) presents a promising cost-effective alternative, leveraging wave propagation models to accurately reconstruct properties from limited data, avoiding local minima pitfalls [34]. This approach may reduce imaging costs while maintaining diagnostic accuracy.

Tailored monitoring strategies are crucial to address variability in disease progression and patient treatment responses. Integrating AI and machine learning models into diagnostic workflows holds promise for enhancing ultrasound image accuracy, which is often affected by variability and noise [27]. Future research should focus on developing AI models capable of handling such variability and integrating multi-parametric data to enhance diagnostic capabilities [27]. Additionally, algorithms leveraging both local and non-local information can improve segmentation accuracy in noisy environments [35].

The gut-liver axis also emerges as a significant factor in tailoring monitoring approaches. Modifications to the gut microbiota may offer therapeutic benefits for both B-HCC and NBNC-HCC patients, highlighting the potential for microbiome-based interventions in personalized treatment plans [24]. Incorporating these insights into tailored monitoring strategies can improve hepatic nodule management, reduce progression to HCC, and enhance patient outcomes while reducing healthcare costs.

5 Imaging Techniques in Nodule Monitoring

5.1 Traditional Imaging Techniques

Traditional imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are essential for monitoring liver nodules in Hepatitis B-related cirrhosis. Ultrasound is widely used for its non-invasive nature, accessibility, and cost-effectiveness, making it suitable for routine surveillance. However, its diagnostic accuracy can be limited by variable image quality due to differing examination conditions, necessitating additional modalities for enhanced precision [27]. CT scans, offering detailed cross-sectional images, excel in identifying hepatic nodules by assessing calcifications and vascular patterns, though their use involves ionizing radiation and contrast agents. MRI, particularly diffusion-weighted imaging (MRI-DWI), provides superior soft tissue contrast, crucial for distinguishing benign from malignant nodules, thus informing clinical management and treatment strategies for hepatocellular carcinoma (HCC) [31, 27, 25, 11]. Contrast-enhanced ultrasound (CEUS) enhances nodule detection by enabling real-time assessment of tumor perfusion and vascular changes [31]. Recent advancements in image segmentation algorithms and metrics like SSEGEP improve diagnostic capabilities by prioritizing smaller segments critical for early detection [30, 27, 26, 35]. Deep learning integration in cancer detection enhances lesion identification accuracy, while AI applications in sonography reduce human error, improving diagnostic precision and enabling personalized care.

As depicted in Figure 4, traditional imaging techniques are crucial for the accurate assessment and management of nodular lesions. The examples highlight microscopy and CT imaging approaches, illustrating the necessary optical components and advancements in imaging detail and focus essential for effective nodule monitoring [36, 35].

5.2 Advanced Imaging Techniques and Technological Integration

Advancements in imaging techniques have improved liver nodule monitoring in Hepatitis B-related cirrhosis, addressing limitations of traditional methods. CEUS provides dynamic tumor perfusion assessments, offering insights into HCC treatment responses and effectively characterizing PEComas [32, 29]. Model-based quantitative ultrasound (MB-QRUS) enhances imaging efficiency and adaptability with high accuracy using limited data [34]. Advanced segmentation algorithms, such as Fuzzy Possibilistic C-Means (FPCM), improve diagnostic precision in noisy conditions [35]. These advancements facilitate accurate risk stratification and personalized management strategies, enhancing surveillance protocols and enabling early HCC detection, crucial for improving patient outcomes [5, 10, 6].

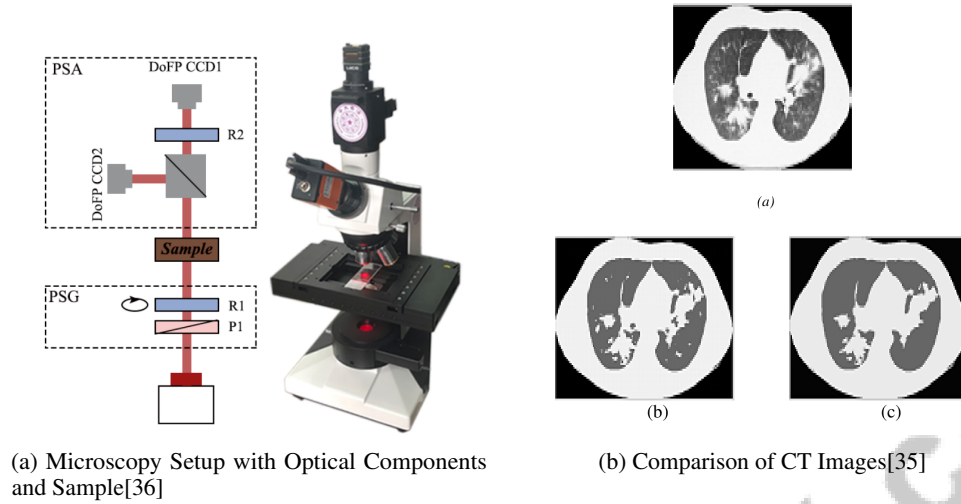


Figure 4: Examples of Traditional Imaging Techniques

5.3 Artificial Intelligence and Machine Learning

Artificial Intelligence (AI) and Machine Learning (ML) are revolutionizing medical imaging, particularly in liver nodule monitoring and diagnosis in Hepatitis B-related cirrhosis. AI and ML integration enhances diagnostic accuracy and efficiency, addressing traditional imaging limitations [30]. Deep learning models, capable of learning complex patterns from medical images, achieve significant advancements in lesion detection accuracy, often matching experienced radiologists' performance [30, 27]. A dual-modality machine learning framework, combining polarization features from Mueller matrix images with radiomics features from HE stained images, exemplifies AI's potential to enhance classification accuracy and diagnostic precision [36]. AI models also mitigate variability and noise in ultrasound images, enhancing analysis robustness and improving liver nodule detection sensitivity and specificity, enabling timely intervention and optimizing patient outcomes [27].

6 Management of Liver Nodules

6.1 Individualized Treatment Plans

Developing individualized treatment plans for liver nodules in Hepatitis B-related cirrhosis is crucial for optimizing therapeutic outcomes and enhancing patient quality of life. This strategy involves a comprehensive evaluation of nodule characteristics, patient health, and HCC stages to tailor treatments to each patient's clinical profile [23]. Surgical resection and liver transplantation are the primary curative options for early-stage HCC, whereas transarterial chemoembolization (TACE) and molecular targeted therapies are effective for intermediate to advanced HCC [29].

Advancements in imaging, particularly contrast-enhanced ultrasound (CEUS), have improved treatment planning by offering real-time assessments of tumor perfusion, aiding in timely treatment adjustments and distinguishing between benign and malignant lesions. Incorporating molecular profiling into clinical practice further personalizes treatment by selecting therapies based on tumor molecular characteristics [22]. Antiviral therapies, notably tenofovir disoproxil fumarate (TDF), play a vital role in reducing HCC risk, underscoring their inclusion in individualized care plans [23].

Multidisciplinary collaboration among hepatologists, oncologists, radiologists, and other specialists is essential for formulating optimal treatment plans that integrate clinical and molecular profiles. Additionally, the gut microbiota offers potential biomarkers for liver disease progression, with specific bacterial taxa linked to various HBV infection stages. These insights suggest novel therapeutic targets and underscore the potential for microbiome research in personalized treatment strategies [24]. Integrating these findings allows clinicians to enhance personalized therapeutic approaches, improving outcomes for patients with Hepatitis B-related cirrhosis and liver nodules.

6.2 Decision-Making Frameworks

Effective management of liver nodules in Hepatitis B-related cirrhosis requires robust decision-making frameworks that integrate diverse diagnostic and therapeutic modalities. These frameworks facilitate comprehensive assessments of clinical data, imaging findings, and molecular profiles, enabling informed decisions about tailored management strategies. This systematic approach enhances diagnostic accuracy and incorporates advancements in imaging technologies, including AI-powered ultrasound, and the evolving role of liver biopsy in HCC management, emphasizing histopathological insights and molecular classifications in guiding targeted therapies [11, 25, 26, 27, 37].

A key component is integrating advanced imaging techniques and radiomics, which provide insights into the morphological and functional characteristics of liver nodules. The fusion of polarization imaging and radiomics features enhances liver cancer classification accuracy, enabling precise differentiation between benign and malignant lesions [36]. This approach underscores the importance of combining complementary imaging modalities to improve diagnostic accuracy and inform treatment decisions.

Decision-making frameworks for HCC highlight the necessity of multidisciplinary collaboration among specialists, including hepatologists, radiologists, and oncologists, to conduct comprehensive evaluations of each patient's clinical condition. This collaborative approach enhances diagnostic accuracy through diverse expertise and facilitates the integration of prognostic and therapeutic insights derived from histopathological and molecular analyses, ultimately improving patient outcomes [16, 25, 11]. By leveraging advanced technologies and a multidisciplinary approach, these frameworks aim to enhance the precision and effectiveness of treatment for patients with Hepatitis B-related cirrhosis.

6.3 Management of Complications

Managing complications from liver nodules and cirrhosis in Hepatitis B-related liver disease presents complex challenges. Complications such as portal hypertension, hepatic encephalopathy, and ascites significantly impact patient quality of life and necessitate comprehensive management strategies. The diverse clinical manifestations of hepatic nodules and the risk of malignant transformation into HCC require rigorous surveillance and prompt interventions to improve outcomes. Given HCC's tendency to present at advanced stages with high recurrence rates, effective monitoring strategies are crucial for early detection and management. Recent advancements in imaging and histopathological techniques emphasize the need for tailored diagnostic approaches, especially for high-risk populations, to inform treatment decisions and enhance prognostic accuracy [7, 25, 21, 11].

Interobserver variability and the subjective nature of imaging interpretations pose significant challenges, leading to inconsistent assessments of liver nodules [31]. This variability underscores the necessity for standardized imaging protocols and the integration of advanced imaging techniques, such as CEUS, which provide real-time evaluations of vascular changes, aiding in the differentiation of benign and malignant lesions.

The management of hepatic PEComas, a rare type of liver tumor, exemplifies the challenges in understanding the long-term behavior of certain nodules and the efficacy of various management strategies. Significant gaps remain in comprehending the malignant potential of PEComas, complicating the formulation of effective treatment plans [29]. Addressing these gaps requires ongoing research and the development of robust clinical guidelines that incorporate both traditional and novel therapeutic approaches.

Moreover, multidisciplinary care teams are essential for addressing the diverse complications associated with cirrhosis and liver nodules. Hepatologists, radiologists, oncologists, and other specialists must collaborate to develop individualized management plans that consider each patient's unique clinical and molecular profiles. This collaborative approach systematically addresses all potential complications related to HCC management, drawing from comprehensive evidence-based guidelines that enhance patient outcomes and improve quality of life by integrating various clinical considerations, including epidemiology, prevention, diagnosis, staging, treatment options, and response assessment tailored to individual patient needs [16, 11, 10, 38, 37].

7 Prevention of Hepatocellular Carcinoma

7.1 Antiviral Therapies

Antiviral therapies play a pivotal role in reducing hepatocellular carcinoma (HCC) risk among patients with Hepatitis B-related cirrhosis. The development of effective antiviral treatments has significantly advanced HCC prevention, particularly for chronic Hepatitis B virus (HBV) infections, by suppressing HBV replication, thereby decreasing liver inflammation and the risk of cirrhosis and HCC [2]. Tenofovir disoproxil fumarate (TDF) is notably effective in minimizing HCC risk, highlighting the importance of selecting potent antiviral agents in clinical practice [38]. Personalized medicine further enhances antiviral therapy effectiveness by tailoring treatments to individual patient profiles and risk factors [38].

HBV vaccination is fundamental in preventing HBV-related HCC, significantly reducing chronic HBV infection rates and HCC incidence [20]. The success of vaccination and antiviral strategies underscores their substantial public health impact, especially compared to progress against HCV-related HCC [20]. Emerging research suggests probiotics may offer additional protection against HCC in patients undergoing antiviral treatment for HBV, with higher probiotic doses linked to reduced HCC risk, indicating a potential adjunctive role in comprehensive prevention strategies [14]. This comprehensive approach leverages the cancer-preventive potential of probiotics, which may restore gut microbiota balance and reduce inflammation, thus lowering HCC risk [20, 14, 24].

The strategic integration of antiviral therapies, vaccination, and adjunctive treatments, such as probiotics, forms a robust approach to HCC prevention in patients with Hepatitis B-related cirrhosis. This multifaceted strategy addresses viral replication suppression through antiviral medications while exploring novel therapeutic avenues, underscoring the necessity for continued research and innovation to refine these strategies and improve patient outcomes.

7.2 Lifestyle Modifications and Vaccination

Lifestyle modifications and vaccination are crucial in preventing hepatocellular carcinoma (HCC) in patients with Hepatitis B-related cirrhosis. Healthy lifestyle practices, including dietary changes, regular physical activity, and reduced alcohol consumption, significantly mitigate risk factors associated with liver disease progression and HCC development by reducing oxidative stress and inflammation [21, 11, 22]. HBV vaccination remains a primary prevention strategy, effectively decreasing HBV infection rates and subsequent HCC risk, particularly in high-endemic regions [20].

In addition to vaccination, lifestyle interventions targeting weight management and metabolic syndrome prevention are vital for reducing non-alcoholic fatty liver disease (NAFLD) risk, which can exacerbate liver damage in HBV-infected individuals. Addressing the interplay between metabolic disorders, such as obesity and NAFLD, and chronic HBV infection necessitates a comprehensive prevention strategy that includes HBV vaccination, antiviral therapies, and lifestyle modifications [16, 2, 20, 21, 22]. Dietary interventions, particularly increased intake of fruits, vegetables, and omega-3 fatty acids, may offer protective effects against liver carcinogenesis by influencing metabolic pathways and reducing inflammation [16, 21, 22, 14, 24].

Integrating lifestyle modifications, such as dietary changes and increased physical activity, with vaccination strategies significantly reduces HCC incidence in patients with Hepatitis B-related cirrhosis. This approach addresses direct viral causes of HCC while mitigating cofactors associated with disease progression, ultimately enhancing antiviral therapy effectiveness and improving patient outcomes [16, 2, 20, 21, 24]. Ongoing public health efforts and patient education are essential for promoting these interventions and improving long-term outcomes for at-risk populations.

7.3 Role of Preventive Strategies

Preventive strategies are essential in reducing hepatocellular carcinoma (HCC) risk among patients with Hepatitis B-related cirrhosis, encompassing interventions such as antiviral therapies, lifestyle modifications, and innovative approaches like probiotic supplementation. These strategies address the multifactorial nature of liver carcinogenesis by integrating early detection through surveillance, managing risk factors like viral hepatitis and NAFLD, and advancing treatment options including locoregional and targeted systemic therapies [25, 16, 21, 11].

Antiviral therapies are foundational in prevention, effectively suppressing Hepatitis B virus (HBV) replication and reducing liver inflammation, crucial in preventing cirrhosis and HCC progression. Personalized medicine strategies enhance the effectiveness of HCC therapies by facilitating customized treatment plans that consider individual patient profiles and risk factors, particularly given the evolving epidemiology of HCC [21, 11]. Implementing lifestyle modifications, such as reducing alcohol consumption, maintaining a healthy weight, and avoiding dietary toxins, further lowers HCC risk by mitigating oxidative stress and inflammation [16, 11, 24].

Emerging research highlights the potential role of probiotics in liver disease prevention, suggesting they may modulate gut microbiota, reduce inflammation, and prevent disease progression [14]. Vaccination against HBV remains a vital strategy, significantly decreasing chronic HBV infection incidence, which accounts for a substantial proportion of HCC cases globally [15, 20, 2]. The success of vaccination programs underscores the importance of public health initiatives in reducing HBV-related liver cancer burden.

The comprehensive integration of antiviral therapies, lifestyle modifications, probiotic supplementation, and vaccination into a unified preventive strategy represents a multifaceted approach to significantly lowering HCC risk in patients with cirrhosis from chronic hepatitis B infection. This strategy addresses HBV's direct effects on liver health while considering gut microbiota alterations and lifestyle factors contributing to disease progression and cancer development. By employing these combined interventions, healthcare providers can enhance patient outcomes and potentially reduce HCC incidence in at-risk populations [9, 2, 20, 14, 24]. Continued research and innovation are essential for refining these strategies and improving patient outcomes.

8 Cirrhosis Progression and Monitoring

Exploring the complexities of cirrhosis progression highlights the multifaceted challenges in monitoring this condition. Liver cirrhosis, a significant outcome of Hepatitis B infection, is linked to high global morbidity and mortality. Key areas include the disease's pathophysiology, the influence of gut microbiota, and management strategy challenges, essential for improving patient outcomes and preventing complications like hepatocellular carcinoma (HCC) [9, 11, 17, 10, 6]. This analysis identifies hurdles in the monitoring process, crucial for effective clinical strategies. We focus on current challenges in monitoring cirrhosis progression, including early detection issues, imaging variability, and the integration of biomarkers and molecular data.

8.1 Current Challenges in Monitoring Cirrhosis Progression

Monitoring cirrhosis progression, especially in Hepatitis B-related liver disease, presents significant challenges impacting clinical management and patient outcomes. A major issue is the asymptomatic nature of early-stage cirrhosis, complicating early detection and often leading to diagnoses at advanced stages [17]. This is exacerbated by a lack of public awareness about cirrhosis, delaying interventions [12].

Traditional imaging techniques, like ultrasound, pose challenges due to variability and subjectivity, affecting accurate assessments of liver fibrosis and cirrhosis progression. Image quality inconsistencies complicate clinical decision-making [27], underscoring the need for standardized protocols and advanced modalities with improved sensitivity and specificity.

Despite their potential, the integration of biomarkers and molecular data into routine monitoring is limited. Identifying reliable biomarkers for liver fibrosis and cirrhosis progression is crucial for developing non-invasive diagnostic tools, reducing reliance on invasive procedures like liver biopsy [22].

Cirrhosis management is further complicated by the rising prevalence of cases due to non-alcoholic fatty liver disease (NAFLD) and alcohol consumption, adding to the burden of liver disease management [17]. The interplay of genetic and epigenetic factors complicates understanding cirrhosis progression, challenging the development of effective monitoring strategies [12].

To improve liver tumor diagnosis, research should focus on enhancing imaging techniques like contrast-enhanced ultrasound (CEUS), which allows real-time evaluation of microvessel perfusion and treatment response. Integrating artificial intelligence (AI) and machine learning into diagnostics

can reduce human error, improve accuracy, and facilitate personalized care through advanced data analysis and classification methods for hepatic lesions [30, 27, 33, 34, 32]. These technologies can enhance imaging analysis accuracy and facilitate early detection of cirrhosis progression, improving patient outcomes. A multidisciplinary approach involving hepatologists, radiologists, and other specialists is vital for developing comprehensive monitoring strategies that consider the diverse clinical and molecular profiles of patients with Hepatitis B-related cirrhosis.

8.2 Biomarkers and Molecular Data Integration

Integrating biomarkers and molecular data into liver health assessment is an emerging frontier in managing Hepatitis B-related cirrhosis. Biomarkers offer a non-invasive means of evaluating liver fibrosis, inflammation, and HCC progression risk. Identifying reliable biomarkers is essential to improve cirrhosis assessment accuracy, minimizing the need for invasive procedures like liver biopsy. Recent studies show that non-invasive serum biomarkers can effectively differentiate HCC from hepatitis B virus-related cirrhosis, suggesting a promising alternative to traditional diagnostics. Risk-stratified surveillance using these biomarkers can enhance patient management and outcomes, indicating a shift towards precise and less invasive diagnostic strategies [10, 22, 11, 4].

Molecular data, including genetic and epigenetic information, offer insights into liver disease pathogenesis and HCC progression. Epigenetic modifications, like DNA methylation and histone modification, significantly influence viral-related carcinogenesis by affecting gene expression and tumor development. Future research should explore these epigenetic factors to better understand their impact on liver health and potential as therapeutic targets [20].

Gut microbiota is emerging as a crucial factor in liver disease progression. Alterations in the gut microbiome correlate with various stages of HBV infection and liver disease, indicating that modifying gut microbiota may have therapeutic potential in HCC management [24]. Trends in microbiome research emphasize understanding gut bacteria and liver health interactions, potentially leading to novel interventions for preventing and treating liver disease.

8.3 Risk Stratification and Surveillance

Risk stratification is essential for effective liver cirrhosis surveillance, particularly in Hepatitis B-related cirrhosis. It involves categorizing patients based on their risk of progression to HCC, enabling tailored monitoring and management strategies. Comprehensive integration of clinical, imaging, and molecular data is crucial for precise risk stratification, facilitating the identification of patients at elevated HCC risk and supporting timely interventions. This multifaceted approach enhances diagnostic accuracy by leveraging advancements in imaging techniques and molecular profiling, revealing prognostic and therapeutic insights not always apparent through traditional histopathology alone. Risk-stratified surveillance strategies tailored to individual risk assessments optimize patient outcomes and improve management of this advanced disease [36, 25, 11, 4].

Advanced imaging techniques, such as contrast-enhanced ultrasound (CEUS) and magnetic resonance imaging (MRI), are pivotal in risk stratification, providing detailed assessments of liver nodules and vascular changes. These modalities offer enhanced sensitivity and specificity in detecting early-stage HCC, crucial for effective surveillance and intervention. Novel imaging metrics, like SSEGEP, further improve nodule characterization accuracy, aiding risk assessment and decision-making [26].

Molecular profiling, including genetic and epigenetic analysis, reveals insights into liver disease progression and HCC development mechanisms. Biomarkers identified through these analyses serve as valuable tools for risk stratification, offering non-invasive means of evaluating disease severity and progression risk [22]. Integrating these molecular insights into clinical practice enhances risk stratification precision, allowing for personalized surveillance strategies aligned with individual patient profiles.

Incorporating artificial intelligence (AI) and machine learning models into risk stratification processes promises to improve surveillance accuracy and efficiency. These technologies use deep learning algorithms to analyze intricate datasets encompassing clinical, imaging, and molecular information. By integrating these diverse data types, they generate detailed risk profiles, significantly enhancing clinical decision-making in oncology, particularly in diagnosing and managing liver tumors like HCC and intrahepatic cholangiocarcinoma (ICC). This comprehensive approach aids accurate lesion

classification and facilitates personalized treatment strategies by predicting patient outcomes based on diagnostic factors [30, 11, 25, 27, 36].

9 Conclusion

This survey underscores the imperative of early detection and comprehensive management in addressing Hepatitis B-related cirrhosis and hepatocellular carcinoma (HCC). The integration of advanced imaging modalities, such as contrast-enhanced ultrasound (CEUS) and magnetic resonance imaging (MRI), has markedly improved diagnostic accuracy, enabling prompt interventions. These technologies, alongside molecular profiling and frameworks like LI-RADS-CEUS, offer promising pathways for standardizing HCC classification, though challenges persist in the precise diagnosis of smaller nodules.

Continued research is vital to elucidate the intricate interplay of genetic, epigenetic, and environmental factors in liver carcinogenesis. Future studies should prioritize the examination of immune checkpoints, novel therapeutic targets, and the refinement of biomarker panels for early HCC detection. Additionally, a deeper understanding of HBV's molecular mechanisms and the development of more sophisticated animal models are essential for advancing prevention and therapeutic strategies.

Preventive strategies, including antiviral therapies and lifestyle modifications, play a crucial role in reducing HCC incidence. The demonstrated efficacy of tenofovir disoproxil fumarate (TDF) in lowering HCC risk, especially in targeted patient groups, emphasizes the importance of integrating these treatments into holistic care plans. Future research should aim to substantiate these outcomes through extensive multicenter trials and explore the potential of various probiotic strains in liver disease management.

The survey further highlights the necessity of robust observational studies to assess long-term virologic responses and the biological mechanisms linked to HCC risk. Moreover, the impact of emerging global health challenges, such as COVID-19, on the prevalence and management of liver diseases, requires thorough investigation.

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