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Hepatocellular Carcinoma in the Twenty-First Century: Risk-Adapted Surveillance, Biomarkers, and Evolving Therapeutic Strategies

Mikołaj Bochnak

University of Rzeszów

al. Tadeusza Rejtana 16C, 35-310 Rzeszów, Poland

<https://orcid.org/0009-0007-9913-8470>

mikolajbochnak@gmail.com

Kinga Skalniak

University of Rzeszów

al. Tadeusza Rejtana 16C, 35-310 Rzeszów, Poland

<https://orcid.org/0009-0009-4752-9351>

bskalniak@gmail.com

Julia Wojtanowicz
University of Rzeszów
al. Tadeusza Rejtana 16C, 35-310 Rzeszów, Poland
<https://orcid.org/0009-0008-0747-9946>
wojtanowiczjulia@gmail.com

Corresponding Author
Mikołaj Bochnak
mikolajbochnak@gmail.com

Abstract

Introduction and Purpose

The growing contribution of metabolic dysfunction-associated steatotic liver disease (MASLD) to hepatocellular carcinoma (HCC) has exposed important limitations of conventional ultrasound surveillance. Obesity, steatosis, and heterogeneous liver parenchyma may impair visualization and reduce the detection of early tumors. This narrative review examines current approaches to HCC risk stratification, surveillance, diagnosis, and treatment, with particular attention to risk-adapted strategies in patients with MASLD.

Materials and Methods

Peer-reviewed publications identified primarily through PubMed were reviewed. The analysis included conventional surveillance, abbreviated magnetic resonance imaging (AMRI), elastography, biomarker-based models, liquid biopsy, algorithm-assisted imaging, and recent developments in locoregional and systemic treatment.

Results

Ultrasound, with or without alpha-fetoprotein, remains the standard surveillance method for patients at high risk of HCC, but its performance is reduced when liver visualization is inadequate. In such patients, alternative imaging, including AMRI, may be considered. Elastography and clinical risk models can help identify patients at increased risk, while biomarker panels such as GALAD may complement imaging. Liquid biopsy, radiomics, and

artificial intelligence-based tools have not yet been sufficiently standardized for routine surveillance. At the same time, advances in locoregional treatment, immunotherapy, and targeted therapy have broadened therapeutic options across several stages of HCC.

Conclusion

The main challenge in HCC surveillance is not to replace ultrasonography universally, but to identify patients in whom it is unlikely to provide reliable assessment. A risk-adapted approach combining clinical risk, ultrasound quality, and selected complementary tests appears particularly relevant in MASLD. Prospective studies are still needed to determine which strategies improve early detection and clinical outcomes.

Keywords: hepatocellular carcinoma, metabolic dysfunction-associated steatotic liver disease, surveillance, abbreviated magnetic resonance imaging, biomarkers, risk stratification

1. Introduction

Hepatocellular carcinoma (HCC) remains a major challenge in hepatology and oncology. Despite advances in imaging, locoregional treatment, and systemic therapy, mortality remains high because many tumors are diagnosed after potentially curative treatment is no longer feasible. Primary liver cancer is the sixth most commonly diagnosed malignancy and the third leading cause of cancer-related death worldwide, with HCC accounting for most cases (1,2). Chronic hepatitis B and C virus infections and alcohol-related liver disease remain important causes, but the contribution of metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing, particularly in Europe and North America (3).

The multisociety consensus published in 2023 replaced the previous NAFLD terminology with an affirmative definition of MASLD based on hepatic steatosis and at least one cardiometabolic risk factor (4). The new terminology emphasizes the close association of steatotic liver disease with obesity, type 2 diabetes, and other metabolic abnormalities. These conditions contribute not only to disease progression but also to the increasing number of patients potentially at risk of HCC (3,5,6).

That population, however, is far from uniform. The risk of HCC is highest in patients with cirrhosis, for whom regular surveillance is recommended. HCC can also occur in non-cirrhotic MASLD, but the absolute incidence in this much larger population is too low to justify universal surveillance. Identifying the smaller subgroup that could benefit from closer

observation remains difficult and is one of the central unresolved questions in MASLD-related HCC.

Ultrasonography, usually performed every six months with or without alpha-fetoprotein measurement, remains the standard surveillance method in patients at high risk. Its performance depends, however, on adequate visualization of the liver (6,7). Obesity, marked steatosis, and a coarse or nodular parenchymal pattern can obscure small lesions, a problem frequently encountered in MASLD-related cirrhosis. Repeatedly inadequate examinations may therefore provide false reassurance rather than effective surveillance. At the same time, conventional risk categories do not fully account for the combined effects of fibrosis severity, age, sex, diabetes, obesity, and other modifiers of HCC risk (6,7).

These limitations have prompted interest in surveillance strategies tailored to both individual risk and ultrasound quality. Abbreviated magnetic resonance imaging, elastography, and biomarker-based models may help refine surveillance in selected patients, whereas liquid biopsy and algorithm-assisted imaging are still being evaluated (5,8,9). The practical challenge is to determine when these methods provide sufficient benefit to justify their additional cost and complexity (2,6).

This narrative review critically examines current and emerging approaches to HCC surveillance and early detection in the era of MASLD. Particular attention is given to the limitations of ultrasound, the identification of patients who may require alternative surveillance, and the evidence supporting risk-adapted combinations of clinical assessment, imaging, and circulating biomarkers.

2. Epidemiology and Risk Factors

The epidemiology of HCC reflects marked geographical differences in the causes of chronic liver disease. HBV remains the predominant risk factor in many parts of Asia and sub-Saharan Africa, whereas HCV has historically accounted for a larger proportion of cases in Japan, North Africa, Europe, and North America. Alcohol-related liver disease also contributes substantially to the global burden, while exposure to aflatoxins remains relevant in selected regions. The expansion of HBV vaccination, improved control of viral transmission, nucleos(t)ide analogue therapy for HBV, and direct-acting antiviral treatment for HCV are gradually reducing virus-related HCC in populations with access to these interventions (6). This decline is not uniform, and viral hepatitis continues to account for a large number of

cases worldwide. Moreover, patients with HCV-related cirrhosis remain at sufficient risk to require continued HCC surveillance after sustained virological response (6).

Against this background, MASLD is becoming an increasingly important cause of HCC. Most affected individuals do not develop advanced liver disease, but a proportion progress through metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis to cirrhosis. This course is variable rather than strictly linear. Among the available clinical measures, fibrosis severity is one of the strongest predictors of liver-related complications and HCC, with the greatest risk observed in patients with cirrhosis (3,5).

HCC may nevertheless occur in non-cirrhotic MASLD. Such cases account for a meaningful proportion of MASLD-related tumors, but this observation must be interpreted in the context of the very large population with non-cirrhotic disease. At an individual level, the annual incidence remains too low to justify routine surveillance of all these patients. The unresolved task is therefore to identify a smaller subgroup whose risk approaches a level at which surveillance could provide clinical benefit (3,6).

Risk is modified by several readily available clinical variables. Older age, male sex, type 2 diabetes, and advanced fibrosis show the most consistent associations with HCC in MASLD (3,5). Obesity and the coexistence of multiple cardiometabolic abnormalities may add to this risk, although their effects are partly mediated through diabetes, inflammation, and fibrosis progression. Alcohol consumption and viral hepatitis can coexist with metabolic liver disease and should not be treated as mutually exclusive etiologies. In clinical practice, cumulative exposure to several risk factors may be more informative than assigning a patient to a single etiological category (3,5).

Genetic variation may explain some of the differences between patients with otherwise similar metabolic profiles. The most consistent evidence concerns the PNPLA3 variant associated with steatotic liver disease progression and HCC. Associations have also been reported for TM6SF2 and MBOAT7, although their independent contribution is less uniform across populations. At present, genetic testing and polygenic risk scores are not sufficiently validated to determine routine surveillance decisions (10).

The likelihood of detecting HCC also depends on the performance of the surveillance method. Clinically relevant ultrasound visualization limitations occur in approximately one-fifth of examinations and are more common in patients with obesity and nonviral cirrhosis (6). These

limitations do not increase the biological risk of tumor development, but they increase the probability that an early lesion will be missed. A clinically useful assessment should therefore consider two related questions: how likely the patient is to develop HCC and whether ultrasonography can reliably detect it.

3. Pathogenesis and Natural History

3.1.Mechanisms of Hepatocarcinogenesis

The development of hepatocellular carcinoma in patients with MASLD results from the interaction of metabolic dysfunction, lipotoxicity, chronic inflammation, fibrogenesis, and genomic instability. This process does not necessarily follow an obligatory sequence from steatosis through MASH and cirrhosis to cancer. Although advanced fibrosis and cirrhosis remain the strongest determinants of HCC risk, malignant transformation may also occur in their absence (3,11).

Lipotoxicity is one of the principal initiating mechanisms. Increased delivery of fatty acids from insulin-resistant adipose tissue, enhanced hepatic lipogenesis, and impaired lipid disposal promote the accumulation of toxic lipid species within hepatocytes. These metabolites induce mitochondrial dysfunction, endoplasmic reticulum stress, oxidative injury, and impaired autophagy. Reactive oxygen species damage proteins, membrane lipids, and DNA, while repeated hepatocyte injury and compensatory proliferation favor the acquisition and selection of oncogenic alterations (11).

Persistent metabolic injury also changes the hepatic immune microenvironment. Damaged hepatocytes release danger-associated molecular patterns that activate Kupffer cells and recruit monocytes, neutrophils, and lymphocytes. Proinflammatory and profibrogenic mediators, including tumor necrosis factor, interleukin-6, and transforming growth factor beta, sustain hepatocellular injury and activate hepatic stellate cells (11,12). Over time, chronic inflammation may coexist with impaired antitumor immunity, allowing transformed hepatocyte clones to survive and expand. Alterations in the gut microbiota and increased intestinal permeability may further amplify inflammation through the gut-liver axis (11,12).

Fibrogenesis contributes to carcinogenesis through more than the accumulation of scar tissue. Activated hepatic stellate cells remodel the extracellular matrix and sinusoidal architecture, increasing tissue stiffness, hypoxia, and angiogenesis. Interactions among hepatocytes,

stromal cells, endothelial cells, and immune cells create an environment that supports clonal selection and tumor progression. Nevertheless, the occurrence of MASLD-related HCC in noncirrhotic livers indicates that persistent metabolic injury, inflammation, and genetic susceptibility may promote carcinogenesis before a fully developed cirrhotic microenvironment is present (3,11).

Insulin resistance and compensatory hyperinsulinemia provide an additional proliferative stimulus through insulin and insulin-like growth factor signaling. Activation of downstream PI3K-AKT-mTOR and RAS-MAPK pathways promotes cellular growth and survival while reducing apoptosis. Variants in genes involved in lipid metabolism, including PNPLA3, may modify susceptibility, although their individual effects are insufficient for routine clinical prediction (10). Epigenetic changes, including aberrant DNA methylation, histone modification, and dysregulated microRNA expression, may further suppress tumor suppressor genes and enhance oncogenic signaling (2,11).

3.2.Natural History

The natural history of MASLD-related HCC is heterogeneous. The predominant pathway involves progression from MASH to advanced fibrosis and cirrhosis, which together create a strongly procarcinogenic environment. An alternative pathway allows HCC to develop before cirrhosis becomes established, particularly in patients with persistent metabolic dysfunction and additional clinical or genetic susceptibility (3,11).

Recognition of these parallel pathways is important for surveillance. Cirrhosis remains the clearest indication for routine HCC surveillance, but its absence does not eliminate risk. The clinical challenge is to identify the small subgroup of noncirrhotic patients whose risk may justify closer assessment without extending surveillance indiscriminately to the entire MASLD population (3,5,6). The principal pathways of MASLD-related hepatocarcinogenesis are summarized in Figure 1.

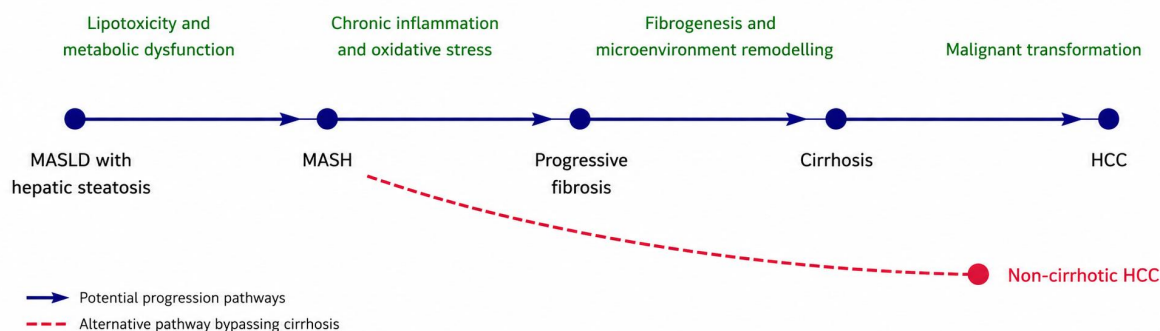


Figure 1. Principal pathways of hepatocellular carcinogenesis in metabolic dysfunction-associated steatotic liver disease. The main pathway involves potential progression from hepatic steatosis through MASH, progressive fibrosis, and cirrhosis to HCC. The dashed line represents an alternative pathway in which HCC develops before cirrhosis becomes established. MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma.

4. Clinical Course and Prognostic Determinants

The clinical course of hepatocellular carcinoma depends on both the malignancy and the underlying liver disease. Deterioration may result from tumor progression, loss of hepatic functional reserve, or a combination of the two. This distinguishes HCC from many other solid tumors and explains why prognosis cannot be assessed from tumor burden alone (2,13,14).

Early-stage HCC is usually asymptomatic. When detected at this stage, the diagnosis commonly results from surveillance rather than from clinical manifestations. Symptoms are generally nonspecific and may include fatigue, loss of appetite, unintentional weight loss, or pain in the right upper quadrant. More advanced disease may present with hepatomegaly, jaundice, declining performance status, or manifestations of portal hypertension and liver failure. In a patient with cirrhosis, new or otherwise unexplained decompensation—such as ascites, hepatic encephalopathy, or variceal bleeding—should raise suspicion of HCC, particularly when accompanied by portal vein invasion or a rapid decline in liver function (2,6,13).

The clinical profile of HCC varies with geographical region and underlying etiology. Patients with MASLD-related HCC are frequently older and have obesity, type 2 diabetes, cardiovascular disease, or other metabolic comorbidities. Some tumors develop before cirrhosis has been recognized, leaving these patients outside conventional surveillance

programs. In such circumstances, HCC may be discovered incidentally or only after symptoms appear. This can reduce the likelihood of diagnosis at a stage suitable for curative treatment, although differences in stage at presentation between etiological groups are not consistent across all studies (3,13).

The untreated course of HCC is highly variable. Increasing tumor size, multifocal or infiltrative growth, macrovascular invasion, extrahepatic spread, declining liver function, and impaired performance status are consistently associated with poorer outcomes (2,13,14). Portal vein tumor thrombosis is particularly important because it reflects aggressive disease, limits several locoregional and surgical options, and may further impair hepatic perfusion.

Cardiometabolic multimorbidity adds another dimension to prognostic assessment in MASLD (3,13). Cardiovascular disease, diabetes-related complications, obesity, sarcopenia, and frailty may increase procedural risk or preclude transplantation, resection, and intensive systemic treatment. Their effect on prognosis may therefore arise not only from tumor biology but also from restricted treatment eligibility and competing causes of death.

The Barcelona Clinic Liver Cancer (BCLC) framework reflects the multidimensional nature of HCC by integrating tumor burden, liver function, and performance status. These variables change over time: treatment may reduce tumor burden, recurrence may alter disease extent, and hepatic reserve may improve or deteriorate independently of tumor response (14). Staging should therefore be repeated at clinically relevant points rather than treated as a fixed assessment made at diagnosis. Multidisciplinary review is particularly important when several treatment options are available or when disease stage and liver function point toward different therapeutic strategies (13,14).

5. Surveillance, Risk Stratification, and Diagnosis

5.1.From Surveillance to Definitive Diagnosis

The pathway to HCC diagnosis includes three distinct stages: surveillance, recall after an abnormal result, and definitive characterization. Surveillance is intended for asymptomatic individuals whose risk is sufficiently high to justify repeated testing (6,13). A suspicious lesion or a relevant change in a biomarker initiates diagnostic evaluation. Ultrasonography and AFP should therefore be viewed as surveillance tools rather than methods that independently confirm or exclude HCC.

Ultrasonography performed every six months, generally combined with serum AFP measurement, remains the standard strategy for most high-risk patients (6,7). Its ability to detect early HCC is influenced by operator experience, body habitus, and liver morphology. Obesity, marked steatosis, and coarse or nodular parenchyma can obscure small lesions, making documentation of visualization quality an essential part of each examination (6).

A new or enlarging lesion measuring at least 1 cm, or a clinically relevant elevation or increase in AFP, should prompt multiphasic contrast-enhanced CT or MRI (6,13). In an appropriate at-risk population, particularly patients with cirrhosis or chronic HBV infection, HCC may be diagnosed without biopsy when characteristic enhancement features are present. These include nonrim arterial-phase hyperenhancement with nonperipheral washout on later phases, interpreted according to lesion size, contrast agent, and the applicable diagnostic criteria (6,13,18). Outside validated high-risk populations, the specificity of these imaging patterns is lower and histopathological confirmation is usually required. Biopsy may also be appropriate when imaging suggests malignancy but is not specific for HCC and the result would influence management (6,13).

5.2.Abbreviated Magnetic Resonance Imaging

Abbreviated MRI uses a limited set of sequences to shorten acquisition and interpretation compared with a complete liver examination. The protocols evaluated to date include noncontrast, dynamic contrast-enhanced, and hepatobiliary-phase approaches; AMRI should therefore not be regarded as a single standardized technique (8).

Meta-analyses have reported per-patient sensitivity of approximately 85–86% and specificity above 90% for the detection of HCC (8). These results are encouraging but should be interpreted cautiously. Many studies were retrospective, used heterogeneous protocols, or included populations with a higher prevalence of focal lesions than would be expected in routine surveillance. Evidence concerning optimal intervals, recall pathways, resource use, and cost-effectiveness is less mature (8).

AMRI is consequently best considered for selected patients rather than as a universal replacement for ultrasonography. Contrast-enhanced MRI, and in some circumstances multiphasic CT, may be used when repeated ultrasound examinations provide inadequate visualization. MRI avoids ionizing radiation but is limited by cost, availability, examination

tolerance, and radiology capacity; repeated CT introduces additional concerns related to radiation and contrast exposure (6,8,13).

5.3.Serum Biomarkers and Multivariable Models

AFP is the most extensively studied serum biomarker for HCC. Its sensitivity for early tumors is incomplete, and elevated concentrations may also accompany hepatic inflammation or regeneration. AFP is therefore more informative when interpreted over time and in conjunction with imaging than as an isolated measurement (6,7).

GALAD is among the best-validated multivariable biomarker models. It combines biological sex, age, AFP, the lectin-reactive AFP fraction (AFP-L3), and des-gamma-carboxy prothrombin (DCP). The original score is calculated as follows:

$$Z = -10.08 + 1.67 \times \text{sex} + 0.09 \times \text{age} + 2.34 \times \log_{10}(\text{AFP}) + 0.04 \times \text{AFP-L3} + 1.33 \times \log_{10}(\text{DCP}) \quad (9),$$

where sex is coded as 1 for males and 0 for females, age is expressed in years, AFP-L3 as a percentage, and biomarker concentrations are entered in the assay units for which the equation was validated. The linear score can be converted into an estimated probability:

$$P(\text{HCC}) = e^z / (1 + e^z).$$

This probability is not universally calibrated across populations. The optimal GALAD cutoff varies with disease etiology, assay platform, HCC prevalence, and the balance sought between sensitivity and specificity. Recent prospective validation indicates that GALAD can improve detection compared with AFP alone, including during the months preceding clinical diagnosis, but its sensitivity for early-stage disease remains insufficient to replace imaging (9,15).

The HCC Early Detection Screening algorithm takes a different approach by incorporating serial biomarker values and clinical variables. Liquid-biopsy techniques, including circulating tumor DNA, methylation signatures, and microRNA profiles, may eventually identify molecular evidence of carcinogenesis before a lesion is visible. At present, low analyte concentrations in early disease, preanalytical variation, and the absence of standardized thresholds restrict their use mainly to research (16,17).

5.4.LI-RADS and Algorithm-Assisted Imaging

The Liver Imaging Reporting and Data System (LI-RADS) standardizes the acquisition, interpretation, and reporting of liver imaging in populations at high risk of HCC. For untreated observations assessed with CT or MRI, categories range from LR-1, indicating definite benignity, to LR-5, indicating imaging features diagnostic of HCC in the appropriate clinical setting. LR-3 and LR-4 represent intermediate probability and probable HCC, respectively. LR-M indicates a malignant lesion without features specific for HCC, while LR-TIV denotes unequivocal tumor within a vein (18).

Indeterminate findings are not managed by category alone. Lesion size, interval growth, liver function, transplant eligibility, and the consequences of obtaining an immediate diagnosis must also be considered (6,13,18). Appropriate options include repeat imaging, use of another modality, biopsy, or multidisciplinary review.

Artificial intelligence is being studied for liver segmentation, lesion detection, radiomic analysis, LI-RADS categorization, and prediction of vascular invasion or treatment response. These applications may reduce workload and improve reproducibility, but their performance often declines when algorithms are tested outside the datasets in which they were developed. Differences in scanners, contrast protocols, patient populations, and reference standards remain important obstacles to routine clinical use (19).

5.5.Elastography and Risk Stratification

Elastography supports fibrosis assessment and HCC risk stratification; it does not diagnose or exclude a focal tumor. Ultrasound-based techniques include vibration-controlled transient elastography, point shear-wave elastography, and two-dimensional shear-wave elastography (5). Higher liver stiffness is associated with advanced fibrosis, cirrhosis, and an increased risk of HCC. The result must nevertheless be interpreted in context because inflammation, cholestasis, congestion, recent food intake, and technical factors can increase measured stiffness independently of fibrosis (5,20).

Magnetic resonance elastography samples a larger proportion of the liver and generally provides more reliable fibrosis assessment, including in many patients with obesity. Its wider use is limited by cost, availability, and the practical constraints of MR (5).I. Neither

ultrasound-based elastography nor magnetic resonance elastography can replace dedicated imaging when malignancy is suspected.

In MASLD, the immediate clinical value of elastography lies in identifying advanced fibrosis and previously unrecognized cirrhosis. Combining liver stiffness with age, diabetes, platelet count, FIB-4, and other clinical variables may refine individual risk estimates. No single stiffness threshold, however, can determine surveillance eligibility across all etiologies. For now, elastography should support decisions based on established clinical risk categories rather than replace them (5,20).

6. Treatment and Emerging Therapeutic Strategies

6.1. Staging and Assessment of Liver Function

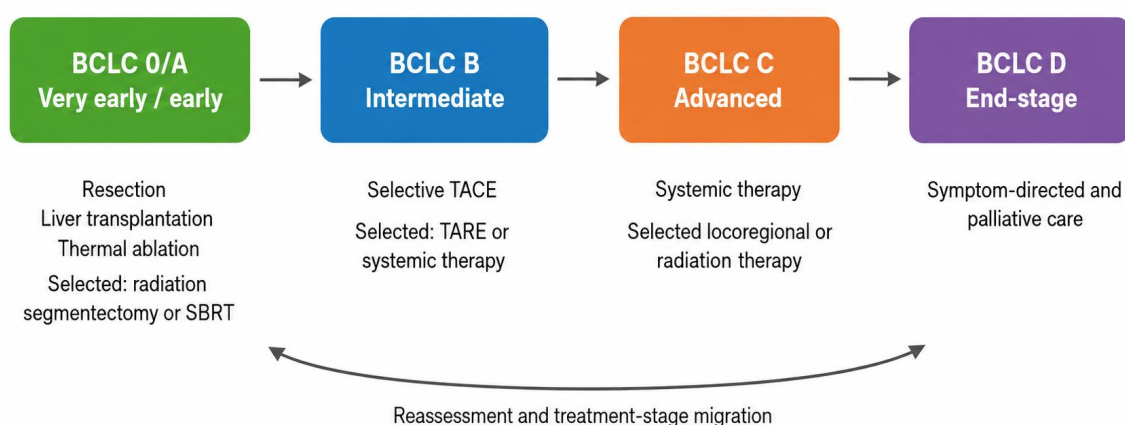
Treatment selection in HCC depends on tumor burden, liver function, performance status, comorbidities, technical feasibility, and transplant eligibility. Because these factors may change during the course of disease, decisions should be made by a multidisciplinary team and reassessed after treatment or clinically relevant deterioration (13,14).

The Barcelona Clinic Liver Cancer (BCLC) strategy integrates tumor stage, liver function, and performance status with prognostic estimates and general treatment recommendations. It distinguishes very early, early, intermediate, advanced, and end-stage disease, while allowing individualized decisions and treatment-stage migration when the conventional option is unsuitable or ineffective (14). The Child–Pugh classification remains widely used to describe hepatic dysfunction, whereas the Albumin–Bilirubin (ALBI) score provides an objective estimate based on serum albumin and bilirubin. These tools are complementary and should not be used in isolation to determine treatment eligibility (13,14).

Table 1. Principal systems used to assess HCC stage and hepatic functional reserve

System	Domain	Components	Clinical role
BCLC	Tumor stage and prognosis	Tumor burden, vascular invasion, extrahepatic spread, liver function, and performance	Links disease stage with general treatment strategies

		status	
Child–Pugh	Hepatic dysfunction	Bilirubin, albumin, INR, ascites, and encephalopathy	Widely used but includes subjective variables
ALBI	Hepatic functional reserve	Albumin and bilirubin	Objective stratification, particularly useful in patients with preserved liver function



Treatment selection depends on tumor burden, liver function, performance status, comorbidities, and multidisciplinary assessment.

Figure 2. Stage-based therapeutic framework for hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer strategy. Treatment options are assigned according to tumor burden, hepatic functional reserve, performance status, comorbidities, and multidisciplinary assessment. Reassessment and treatment-stage migration allow the therapeutic strategy to be modified in response to disease progression, treatment efficacy, toxicity, and changes in liver function. BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; SBRT, stereotactic body radiotherapy.

Source: European Association for the Study of the Liver (13) and Reig et al. (14).

6.2. Curative-Intent Treatment

Potentially curative options include liver resection, transplantation, and local ablation. Resection is preferred for localized HCC in a noncirrhotic liver and may also be considered in selected patients with compensated cirrhosis, sufficient future liver remnant, and acceptable

portal hypertension-related risk. Clinically significant portal hypertension is an important adverse factor but does not exclude limited resection in every patient, particularly at experienced centers (13,14).

Liver transplantation treats both the tumor and the underlying cirrhotic liver. The Milan criteria remain the principal reference standard, although AFP concentration, response to bridging therapy, successful downstaging, and validated expanded criteria may also influence eligibility (13,21). Thermal ablation using radiofrequency or microwave energy is effective for small tumors, with the most reliable local control achieved in lesions up to approximately 3 cm (13). Radiation segmentectomy or SBRT may provide local control with curative intent in selected patients when surgery or thermal ablation is not feasible (13,14).

6.3. Locoregional Treatment

Transarterial chemoembolization remains a standard option for appropriately selected patients with intermediate-stage HCC, preserved liver function, and tumor burden suitable for selective arterial treatment. BCLC B disease is heterogeneous, however, and not every patient benefits from repeated TACE. Extensive tumor burden, deteriorating hepatic reserve, or a low probability of meaningful response should prompt consideration of systemic therapy (13,14).

Transarterial radioembolization using yttrium-90 microspheres may be used for radiation segmentectomy, disease control, downstaging, or bridging to transplantation (13,14). Its limited embolic effect allows treatment of selected patients with portal vein tumor thrombosis, although vascular invasion alone does not constitute an indication for TARE. External-beam radiotherapy, particularly SBRT, is another option for tumors unsuitable for surgery, ablation, or transarterial treatment (13,14).

6.4. Systemic Therapy

Systemic therapy is used for most patients with advanced HCC and for selected patients with intermediate-stage disease who are unsuitable for or no longer benefit from locoregional treatment (13,14,25). Evidence is strongest for patients with Child–Pugh A liver function and good performance status, as these individuals constituted most participants in pivotal clinical trials (13,25).

Preferred first-line regimens include atezolizumab plus bevacizumab, the STRIDE regimen of a single priming dose of tremelimumab combined with durvalumab, and nivolumab plus ipilimumab (22,23,25). The latter became a first-line option after the CheckMate 9DW trial and its 2025 approval in the United States for unresectable or metastatic HCC (24). Selection among these regimens should consider bleeding risk, autoimmune disease, transplant history, cardiovascular comorbidity, and the ability to tolerate immune-related toxicity. Before atezolizumab plus bevacizumab is started, the risk of gastrointestinal bleeding should be assessed and high-risk gastroesophageal varices managed appropriately (13,25). Durvalumab monotherapy, sorafenib, or lenvatinib remain alternatives when combination therapy is unsuitable (13,25).

The optimal sequence after first-line immunotherapy has not been established. Tyrosine kinase inhibitors are commonly used, but supporting evidence is largely based on nonrandomized studies or extrapolation from trials conducted after sorafenib. Options may include sorafenib or lenvatinib if not previously administered, cabozantinib, regorafenib after prior sorafenib, and ramucirumab in patients with AFP concentrations of at least 400 ng/mL. The choice depends on prior treatment, liver function, toxicity, comorbidities, and regional approval (25).

6.5.MASLD and Treatment Selection

Patients with MASLD-related HCC frequently have obesity, type 2 diabetes, cardiovascular disease, chronic kidney disease, or frailty (3,13). These conditions may increase perioperative risk, restrict transplant eligibility, and influence the safety of antiangiogenic treatment. Experimental data have raised the possibility that HCC etiology affects the response to immunotherapy, but clinical evidence remains inconsistent. MASLD alone should therefore not be used as a reason to withhold an immune-checkpoint inhibitor (25,26).

6.6.Emerging Precision-Medicine Strategies

Circulating tumor DNA may provide information on tumor mutations, methylation patterns, treatment response, and recurrence after curative-intent therapy. Detectable postoperative ctDNA has been associated with a higher risk of recurrence, but limited sensitivity in early disease and substantial assay heterogeneity prevent its routine use. Selecting adjuvant treatment according to molecular residual disease remains investigational (17).

Molecular imaging with FAPI- or PSMA-targeted tracers is also under investigation, particularly because conventional FDG-PET has limited sensitivity for well-differentiated HCC (27). Early results suggest possible diagnostic and theranostic applications, but neither approach can replace established CT or MRI staging (28). The microbiome, glypican-3-directed cellular therapies, and personalized neoantigen vaccines represent additional research directions (29). Their evidence is currently limited to observational or early-phase studies, and they should not influence routine treatment decisions outside clinical trials (30,31).

7. Prognosis

Prognosis in HCC is determined by tumor stage, liver function, performance status, and the feasibility of effective treatment. A single population-level survival estimate obscures the marked differences between clinical stages (1,2,13). Patients diagnosed with very early or early HCC may achieve long-term survival after curative-intent treatment, whereas vascular invasion, extrahepatic spread, or hepatic decompensation substantially worsen outcomes. Five-year survival after transplantation within accepted selection criteria often exceeds 70%, while resection and ablation may also provide durable disease control in appropriately selected patients, although recurrence remains common (2,13,21).

In MASLD-related HCC, older age, cardiovascular disease, diabetes, obesity, and frailty may restrict access to surgery, transplantation, or intensive systemic therapy and increase competing mortality (2,13,14). Available evidence does not, however, establish that MASLD-related tumors are intrinsically more aggressive than HCC arising from other causes. Earlier detection, appropriate treatment sequencing, and repeated assessment of both tumor status and liver function remain the principal modifiable determinants of outcome (3,13).

8. Conclusion

The increasing contribution of MASLD to HCC changes both the population requiring surveillance and the performance of conventional screening methods. Ultrasonography with AFP should remain the reference surveillance strategy, but visualization quality must be assessed rather than assumed. When repeated examinations are inadequate, alternative imaging—particularly abbreviated or contrast-enhanced MRI—may be justified in selected patients.

The central challenge is not to replace ultrasonography in every patient, but to identify those in whom it is unlikely to provide reliable surveillance. Fibrosis assessment, clinical risk factors, and biomarker-based models may support this decision. Liquid biopsy and artificial intelligence are promising research tools, but the available evidence does not yet support their routine use.

Improved outcomes will depend on linking risk-adapted surveillance with timely, multidisciplinary treatment. In the growing MASLD population, the most practical path forward is a stepwise strategy that considers both the probability of developing HCC and the ability of the chosen method to detect it at a treatable stage.

Disclosure

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Author's contribution

Conceptualization – Mikołaj Bochnak, Kinga Skalniak, Julia Wojtanowicz

Formal analysis – Kinga Skalniak, Julia Wojtanowicz

Investigation – Mikołaj Bochnak, Kinga Skalniak

Data curation – Mikołaj Bochnak, Julia Wojtanowicz

Writing – rough preparation – Mikołaj Bochnak, Kinga Skalniak, Julia Wojtanowicz

Writing – review and editing – Mikołaj Bochnak, Kinga Skalniak, Julia Wojtanowicz

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