

Opinion

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The multiparametric therapeutic hierarchy: a multidisciplinary approach to HCC management

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Abstract

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related deaths worldwide, characterised by significant clinical heterogeneity and therapeutic complexity. The Barcelona Clinic Liver Cancer system has long been the primary framework for staging and treatment allocation; however, its 2025 update, while introducing important refinements, retains the structural limitations inherent to stage-based algorithms. Recent guidelines from international organisations - including the European Association for the Study of the Liver (2025), the European Society for Medical Oncology (2025), the American Association for the Study of Liver Diseases (2023), and various national bodies - have shifted towards flexible, patient-centred approaches that emphasise multidisciplinary tumour board decision making, feasibility assessment, and dynamic therapeutic adaptation. The multiparametric therapeutic hierarchy (MTH) has been introduced as an expert opinion framework to formalise



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this evolving approach. MTH maintains the prognostic value of staging while separating it from treatment decisions, replacing inflexible algorithms with a tri-axial model: an ordinal hierarchy of therapies ranked by survival benefit, a structured multiparametric feasibility assessment, and a converse therapeutic hierarchy allowing upward movement through curative-intent strategies over time. The model aligns with the conceptual and methodological directions of current guidelines, offering an auditable, adaptable, and ethically consistent decision-making tool for expert multidisciplinary teams. Although based on strong evidence supporting its conceptual foundations, MTH remains a “checklist” that requires prospective validation and additional detail with evidence-based parameters, including biomarkers, imaging criteria, patient-reported outcomes, and integration of artificial intelligence. By providing the conceptual basis for this Special Issue “The Multiparametric Therapeutic Hierarchy: A Multidisciplinary Approach to HCC Management”, MTH aims to support a coherent, multidisciplinary, and future-oriented framework for personalised management of HCC.

Keywords: Hepatocellular carcinoma, multiparametric therapeutic hierarchy, converse therapeutic hierarchy, multidisciplinary tumour board

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide and is characterised by heterogeneous clinical behaviour and significant therapeutic complexity^[1]. Over the past two decades, the Barcelona Clinic Liver Cancer (BCLC) staging algorithm has been the most widely used framework for prognostic classification and treatment selection^[2]. By linking tumour burden, liver function, and performance status to stage-specific therapies, it has provided a pragmatic and standardised approach, facilitating both global dissemination and harmonisation of clinical trial design.

The 2022 and 2025 BCLC updates^[2,3] have introduced several significant improvements, including more detailed staging and expanded treatment options for some patients in intermediate and advanced stages [Table 1]. Additionally, the addition of the clinical decision-making and Complexity, Uncertainty, Subjectivity, Emotion (CUSE) sections has formalised the concept of treatment stage migration within the algorithm as a decision made by the multidisciplinary tumour board (MDT)^[2,3]. Nonetheless, BCLC, also in its 2025 version^[3], maintains some inherent limitations^[4].

The BCLC and other stage-based systems^[4] often promote therapeutic assignments based on average prognosis, frequently overlooking interindividual variability in biological behaviour, comorbidities, technical feasibility, and institutional resources. Patients classified within the same stage may vary considerably in therapeutic potential^[5]. Meanwhile, some are excluded from curative-intent strategies solely based on rigid criteria rather than a more granular feasibility analysis^[4].

In response to these limitations, recent updates from major scientific societies - including the 2025 editions of the European Association for the Study of the Liver (EASL) and the European Society for Medical Oncology (ESMO) guidelines^[1,6] - have embraced a more dynamic, patient-centred approach. These documents emphasise the role of MDTs, stage migration, and structured reassessment, signalling a transition from fixed stage-treatment maps to a logic of therapeutic adaptability.

In light of this evolving context, the multiparametric therapeutic hierarchy (MTH) has been proposed as a conceptual and methodological framework to facilitate ethically consistent, evidence-based, and context-sensitive decision making in HCC^[4,5]. The MTH does not undermine the significance of staging but rather repositions it, shifting it from being the primary driver of therapy to one of several variables within a broader, hierarchical treatment rationale. It introduces a three-axis model to guide treatment selection [Figure 1]:

Table 1. Comparative overview: BCLC 2022 and 2025 vs.MTH

Domain	BCLC 2022 and 2025 - strengths	BCLC 2022 and 2025 - limitations	Multiparametric treatment hierarchy - advantages
Staging and prognosis	Adds ALBI, MELD, AFP; sub-classifies BCLC B (B1-B3); useful for staging and trial design	Prognostic variables not weighted in real-world cohorts; all single nodules in BCLC A; PS 1 = advanced; no vascular invasion subtyping; ignores hepatic vein/biliary invasion; limited for personalised prognosis	Uses staging as contextual tool; supports alternative models (e.g., ITA.LI.CA); improves individual prognostic accuracy
Treatment allocation	Expands first-line options in BCLC B; enables stage migration; allows multiparametric input	Curative options underused in multinodular/vascular-invasive cases; treatment still stage-driven; MDT role reactive; multiparametric evaluation not formalised	Removes rigid algorithm; hierarchical approach favours optimal initial therapy; structured feasibility checklist prevents overtreatment
Methodological framework	Literature-based updates improve stratification and staging logic, and increase treatment personalisation using the CUSE framework	Does not integrate robust observational evidence supporting treatment hierarchies and feasibility models; the CUSE framework is activated only when the algorithm does not provide a first treatment choice and lacks a robust methodological basis	GRADE-aligned: includes high-quality non-RCT evidence; considers values, feasibility, equity, cost-utility, acceptability

BCLC: Barcelona Clinic Liver Cancer; ALBI: albumin-bilirubin; MELD: model for end-stage liver disease; AFP: alpha-fetoprotein; PS: performance status; ITA.LI.CA: Italian Liver Cancer; CUSE: Complexity, Uncertainty, Subjectivity, Emotion; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; RCT: randomised clinical trial; MTH: multiparametric treatment hierarchy; MDT: multidisciplinary tumour board.

- (1) A vertical ordinal hierarchy of therapies ranked by survival benefit.
- (2) A multiparametric horizontal assessment of clinical and logistic feasibility.
- (3) A second vertical axis that illustrates the converse therapeutic hierarchy, enabling patients to advance upward over time based on reassessment.

This expert opinion article refines the MTH framework by developing the three thematic areas summarised in [Table 1](#), and by examining its convergence with contemporary international guidelines. As the introductory paper of this Special Issue on multidisciplinary HCC management, it also serves as the conceptual foundation for the subsequent contributions, which will explore in detail the parameters of the horizontal axis and the clinical application of the converse therapeutic hierarchy [[Figure 1](#)].

STAGING AND PROGNOSIS

Traditional staging systems, such as the BCLC model, have historically served a dual purpose in managing HCC: stratifying prognosis and guiding first-line treatment allocation^[7,8].

This dual purpose has supported global adoption and standardisation in clinical trial design. The 2022 and 2025 BCLC updates mark a significant advancement^[2,3], introducing recognised prognostic modifiers such as alpha-fetoprotein (AFP), albumin-bilirubin (ALBI) grade, and the Model for End-stage Liver Disease (MELD) score, alongside a three-tier sub-classification of the intermediate stage (B1-B3). These refinements increase staging detail, improve patient selection for trials, and recognise the heterogeneity of the intermediate stage.

Despite these advances, fundamental limitations remain. The attempt to use the same variables for both prognosis and treatment allocation is conceptually problematic: prognostic modelling aims to predict the natural history of disease in the absence of intervention, while treatment selection must integrate feasibility, anticipated therapeutic efficacy, and safety - often independently of baseline prognostic factors^[4,5,9].

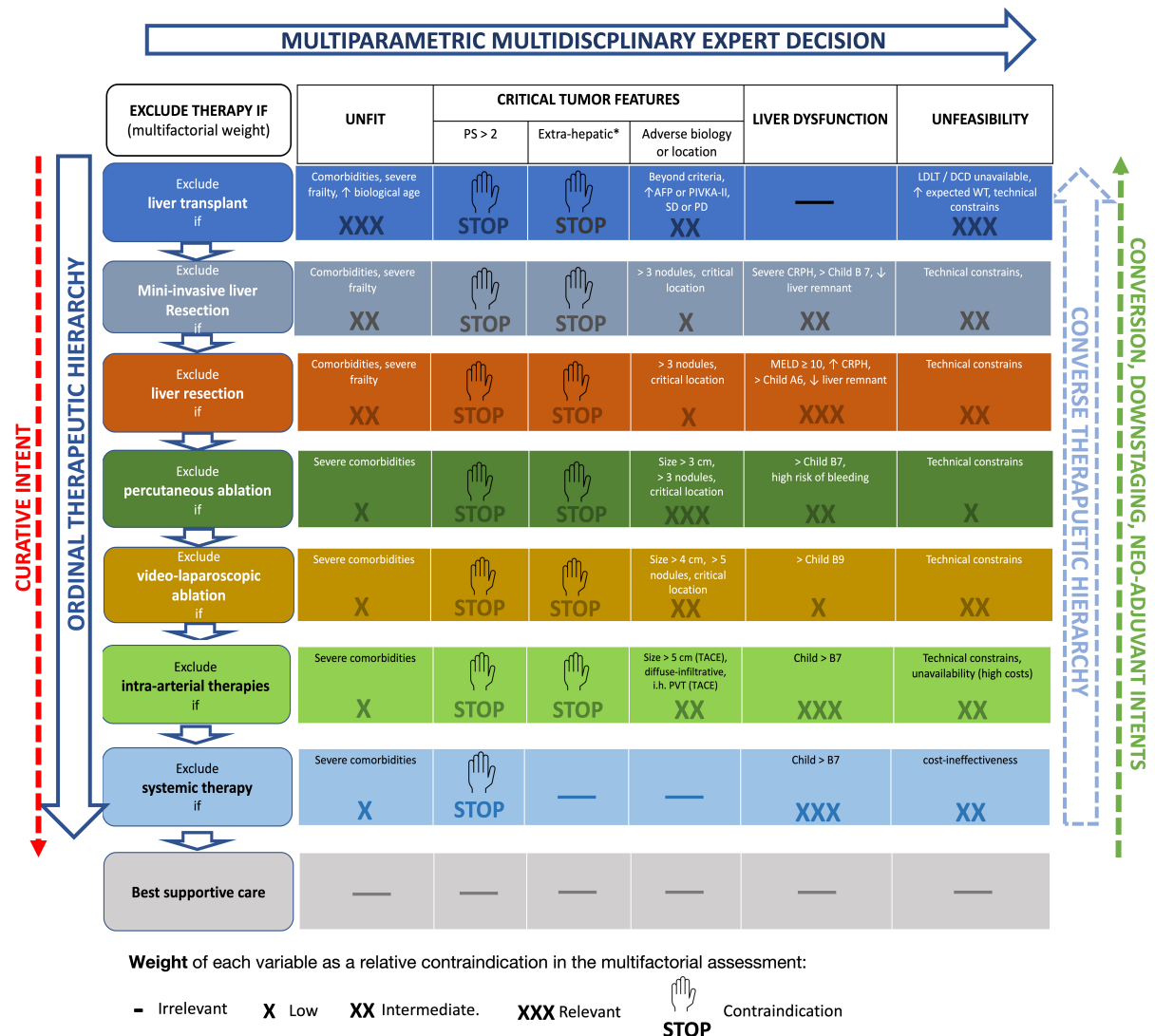


Figure 1. Multiparametric therapeutic hierarchy and clinical therapeutic intents. The concept of the converse therapeutic hierarchy is depicted with a dashed and faded arrow, as the evidence supporting this concept remains weak. Adapted from Vitale et al.^[5] © 2023 Elsevier. Adapted with permission. All rights reserved. AFP: Alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence II; LDLT: living donor liver transplantation; DCD: donor after circulatory death; DBD: donor after brain death; MELD: model for end-stage liver disease; CRPH: clinically relevant portal hypertension; TACE: transarterial chemoembolisation; PVT: portal vein thrombosis; PS: performance status; SD: stable disease; PD: progressive disease.

The BCLC's attempt to merge these functions results in the omission or underrepresentation of critical prognostic factors, such as AFP, which, despite having limited therapeutic implications, possesses strong prognostic relevance^[10]. This results in a model that is systematically underpowered to provide personalised survival estimates or support longitudinal clinical decision making.

The development approach of the BCLC algorithm further diminishes its predictive ability. As an “evidence-based” staging system, it was created through expert consensus and the synthesis of randomised controlled trial (RCT) data, rather than through prognostic modelling in large, real-world populations of

patients with HCC^[9]. Consequently, its categorical variables are not weighted according to their statistical significance in terms of their impact on survival. For example, categorising all patients with a performance status of 1 as advanced-stage fails to capture patient variability and leads to exaggerated risk estimation^[11]. Similarly, including all single nodules, regardless of size or proximity to vessels, within BCLC-A ignores important prognostic differences^[12]. The lack of a detailed assessment of liver dysfunction (Child-Pugh A vs. B) and the failure to differentiate between intrahepatic and extrahepatic vascular invasion further diminish the model's prognostic accuracy^[13].

Thus, while the BCLC staging remains useful for population-level benchmarking and research trial stratification, it lacks individual-level prognostic accuracy [Table 1].

In contrast, the MTH model reconceptualises staging as informative yet non-prescriptive, embracing a paradigm shift in the function of HCC staging systems. Rather than employing staging as a rigid algorithm for treatment assignment, MTH repositions it as a contextual tool for multidisciplinary deliberation. Staging informs but does not dictate therapeutic decisions.

It accommodates superior staging tools such as the Italian Liver Cancer (ITA.LI.CA) prognostic system^[9]. It incorporates biomarkers (AFP), liver function metrics (ALBI, MELD), and characteristics of portal hypertension into a dynamic prognostic framework independent of therapeutic constraints. This is particularly important in real-world populations, where binary cutoff-based stratification (e.g., Child-Pugh A vs. B) often fails to reflect clinical granularity, including subtle portal hypertension, segmental vascular invasion, or sarcopenia. Furthermore, unlike BCLC, MTH explicitly acknowledges that staging should evolve with clinical trajectories, allowing for reassessment and longitudinal optimisation^[5].

Thus, the MTH's prognostic superiority arises from its capacity to integrate more effective staging systems and its conceptual independence between prognosis and therapy - a distinction that the BCLC model cannot structurally achieve^[4].

TREATMENT ALLOCATION

Historically, treatment allocation in HCC has been guided by stage-based paradigms such as the BCLC algorithm [Table 1], where each stage is associated with a recommended first-line therapy. This approach has provided clarity and consistency, particularly for clinical trials, but it can also be rigid^[4]. By closely linking stage and therapy, it risks undertreatment - excluding patients who might benefit from more effective options - and overtreatment - administering aggressive interventions to patients unlikely to tolerate or benefit from them^[5]. The MTH breaks this link, replacing a stage-driven approach with a three-axis framework that emphasises strategy over static categorisation [Figure 1 and Table 1].

Ordinal therapeutic hierarchy (vertical axis)

Treatments are ranked by survival benefit - transplant, resection, ablation, intra-arterial therapies, systemic treatments - while rejecting the rigid division between curative and palliative approaches^[14]. All modalities may have curative potential if applied in the appropriate context. This framework also functions as a timeline of feasibility: delays can lead to irreversible loss of opportunity through untreatable progression or early hepatic decompensation. Untreatable progression refers to disease or clinical deterioration that renders further treatment unfeasible^[3,15-18], while early hepatic decompensation can abruptly disqualify patients from future therapies despite a stable tumour burden^[19,20]. These risks highlight that de-escalation cannot always be delayed without consequence. Clinicians must act within optimal windows, anticipating decline before it occurs. A holistic approach to patients with HCC is essential to safeguard liver function,

with aetiological treatment and adequate management of the underlying liver disease, to improve both the application of potential therapies for HCC and non-HCC-related survival^[21]. Thus, the MTH model emphasises the timely delivery of the most effective feasible therapy, balancing ambition with clinical realism to avoid missed opportunities. The vertical axis is best viewed as a therapeutic ladder and a dynamic timeline that requires careful sequencing and reassessment.

The MTH ordinal axis is flexible and can incorporate future evidence-based novel therapeutic strategies. For example, it could also include emerging immunomodulatory approaches, such as myeloid-derived suppressor cell (MDSC)-targeted therapies, which aim to reverse tumour-induced immunosuppression and enhance response to systemic immunotherapy^[22,23].

Multiparametric feasibility assessment (horizontal axis)

Feasibility is assessed through a structured, multidisciplinary evaluation covering:

- Patient factors: comorbidities, frailty, functional reserve.
- Tumour factors: size, number, biology (AFP, growth rate).
- Liver function: Child-Pugh, ALBI, MELD, hepatic vs. pressure gradient (HVPG)^[24], and liver stiffness^[25,26].
- Technical/logistic factors: anatomy^[27], access to expertise, resources^[28], and patient preferences.

Importantly, this axis emphasises shared expert decision making through the MDT, ensuring that no single parameter arbitrarily excludes or mandates a therapy^[4,5]. Instead, feasibility is viewed as a composite, weighted judgement that balances therapeutic ambition with safety, promoting transparency, documentation, and ongoing reassessment. While optimal implementation benefits from expert MDT deliberation, the MTH framework can also be utilised in settings where MDTs are unavailable (i.e., resource-limited settings such as low- to middle-income countries), providing even a single physician with a structured checklist to ensure all relevant variables are considered in personalised HCC management. From this perspective, MTH potentially reduces - not increases - complex decision-making delays.

This axis will be detailed and refined in some specific papers within this Special Issue.

For example, the recent paper by Lai *et al.* within this Special Issue demonstrates that biomarkers such as AFP and protein induced by vitamin K absence II (PIVKA-II) should not only have prognostic value but also act as dynamic variables that trigger MDT reassessment when relevant thresholds are exceeded^[29].

Additionally, personalised surveillance protocols for patients at high risk of HCC could become part of this axis in the near future^[30].

Converse therapeutic hierarchy (secondary vertical axis)

This axis acknowledges therapeutic plasticity over time^[5]. Patients can advance through the hierarchy via effective therapy - shifting from systemic to surgical treatment, downstaging for transplant, or neoadjuvant approaches^[31]. This axis formalises reassessment and timing as clinical tools, recognising that candidacy for curative-intent therapy can change over time. It includes oncological, technical, and physiological improvements, with the MDT reassessing at each stage to identify and act on new opportunities.

These aspects will be examined in more detail in two specific papers of this Special Issue. One of these has already been published and elaborates on the potential clinical applications of liquid biopsy in the MTH and converse therapeutic hierarchy (CTH) contexts^[29].

This study indicates that biomarkers from liquid biopsies, such as circulating tumour DNA (ctDNA) and exosomal RNA, may be crucial for improving dynamic reassessment. Incorporating these markers is a promising approach to detecting minimal residual disease, forecasting early recurrence, and selecting candidates for therapeutic escalation. Although current evidence remains preliminary, their potential naturally aligns with the MTH and CTH frameworks, particularly in high-expertise MDT environments^[29].

METHODOLOGICAL FRAMEWORK

Contrary to criticisms that the MTH lacks an evidence-based foundation due to its limited reliance on RCTs^[32], the MTH model is arguably more aligned with contemporary standards of evidence evaluation as defined by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework^[33,34].

While the BCLC 2022 and 2025 updates represent progress - integrating new prognostic factors and refining intermediate-stage stratification - it remains primarily built on RCT-derived evidence and expert consensus, with limited incorporation of real-world prognostic modelling^[2,3].

In contrast, MTH draws from the full spectrum of high-quality evidence, including well-designed observational studies, registries, and real-world cohorts. This broader evidence base reflects the GRADE principle that certainty of evidence is not limited to randomised trials, particularly in complex, multidisciplinary contexts such as HCC.

Furthermore, MTH includes other GRADE determinants for recommendation strength: patient values and preferences; feasibility and resource availability; cost-effectiveness and equity of access. This approach recognises that optimal treatment is not solely determined by disease stage or trial eligibility but also by context, priorities, and system capacity.

Overall, the MTH model arguably surpasses the BCLC in methodological rigour and transparency, offering a more robust foundation for personalised treatment decisions. This is exemplified by recent national and international guidelines - most notably the Italian multidisciplinary guidelines^[35], which were fully developed using the GRADE system, alongside the latest EASL^[1] and British guidelines^[36] - that embrace multiparametric evaluation, dynamic reassessment, and real-world adaptability. These documents share core methodological and conceptual principles with MTH, reinforcing its scientific credibility and clinical utility.

INTERNATIONAL GUIDELINES SHIFT TOWARDS MTH AND AWAY FROM ALGORITHMIC BCLC

In recent years, major international guidelines have gradually shifted away from the rigid treatment algorithm traditionally associated with the BCLC staging system, instead adopting principles that are core to the MTH [Table 2 and Figure 2].

The ESMO (2025)^[6] and AASLD (2023)^[37] guidelines retain BCLC staging as a prognostic classification tool but replace its single-pathway algorithm with an alternative treatment stage model. This approach retains stage definitions while providing various therapeutic options within each stage or substage, selected based on feasibility, expertise, and patient considerations.

Table 2. Convergence of International Guidelines with MTH

Guideline	BCLC staging	BCLC algorithm	Role of MDT	Methodological alignment with MTH
ESMO 2025	Maintained	Replaced by treatment stage alternatives	Central, initiates decision	High
AASLD 2023	Maintained	Replaced by treatment stage alternatives	Central, assesses feasibility	High
British Guidelines	Not included	Absent	Central, guides decisions	High
EASL 2025	Maintained	Absent	Primary decision-maker	Very high
Italian Guidelines	Maintained	Absent	Primum movens of care	Very high

MTH: Multiparametric therapeutic hierarchy; BCLC: Barcelona Clinic Liver Cancer; MDT: multidisciplinary tumour board; ESMO: European Society of Medical Oncology; AASLD: American Association for the Study of the Liver; EASL: European Association for the Study of the Liver.

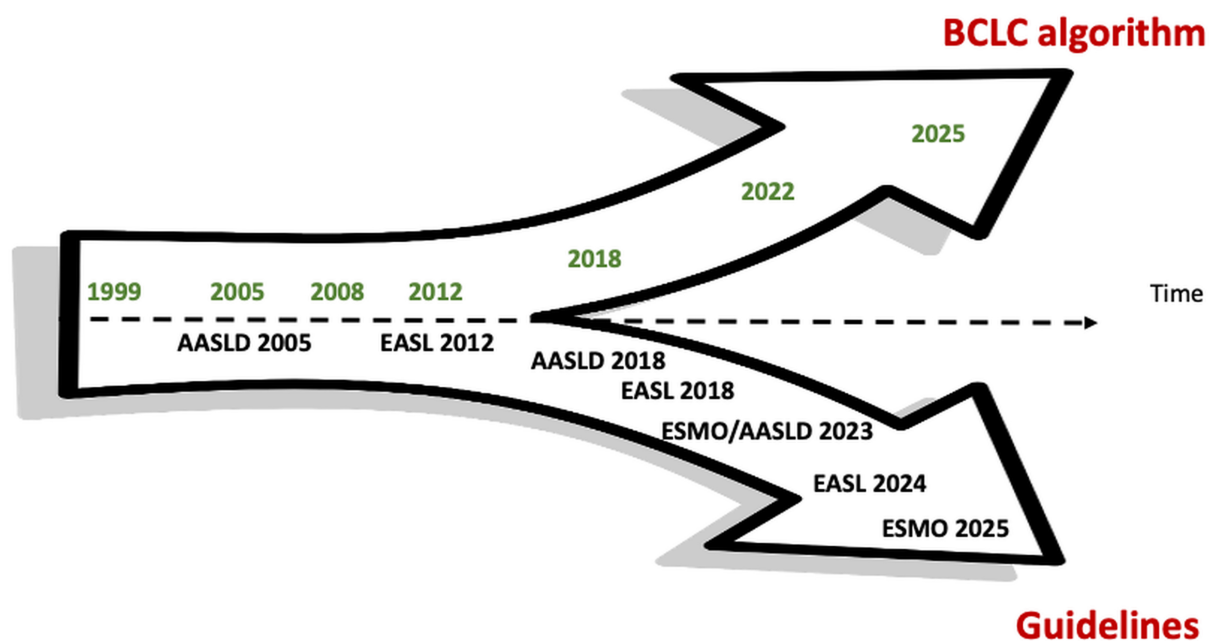


Figure 2. Conceptual evolution in HCC management, progressing from stage (monoparametric) to therapeutic (multiparametric) hierarchy. The various versions of the BCLC algorithm are shown as years in green. HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; ESMO: European Society of Medical Oncology; AASLD: American Association for the Study of the Liver; EASL: European Association for the Study of the Liver.

The British^[36] and Italian guidelines^[35] go further, detaching from BCLC staging entirely in treatment planning, and adopting frameworks that prioritise multidisciplinary deliberation, continuous reassessment, and real-world feasibility. The latest EASL guidelines^[1] mark the clearest break, abandoning algorithmic flowcharts altogether in favour of expert MDT-led, patient-specific therapeutic planning from the outset - precisely the methodological structure codified by MTH.

In this evolving context, the MDT is no longer simply a reactive arbiter of “downward” stage migration but now acts as the primary catalyst for an upward, adaptable, and personalised therapeutic journey. The MTH tri-axial model - incorporating ordinal efficacy ranking, multiparametric feasibility assessment, and dynamic upward adaptability - encompasses this shift, providing a practical and auditable framework that closely aligns with both current and emerging consensus [Table 2]. As shown in Figure 2, the trajectory of

guideline evolution indicates a steady shift away from prescriptive, single-path algorithms towards flexible, MDT-driven strategies - confirming both the clinical relevance and future compatibility of the MTH model.

CONCLUSIONS AND FUTURE DIRECTIONS

This expert opinion review outlines the conceptual framework of the MTH as a structured yet adaptable model for HCC decision making. MTH is based on solid evidence supporting its core principles^[5] - distinguishing prognostic staging from treatment allocation, assessing multiparametric feasibility, and enabling dynamic reassessment through the Converse Therapeutic Hierarchy^[4] - while recognising that it is currently a conceptual “box” or checklist for expert MDTs. Currently, the MTH should be considered a conceptual framework, although based on robust conceptual evidence, that requires prospective validation through multicentre real-world studies before it can be fully implemented as a clinical decision-making tool. Specifically, it ought to be augmented with increasingly detailed, evidence-based parameters, including emerging biomarkers, imaging techniques, and patient-reported outcomes. Ongoing collaborative studies aim to evaluate the MTH framework in real-world, multicentre environments^[38].

Adopting artificial intelligence protocols and developing pragmatic trials within the MDT context will be crucial to this process^[39-41]. Furthermore, future research should concentrate on quantifying the impact of MTH-driven decisions on survival, quality of life, cost-effectiveness, and health equity.

Recent international guidelines from EASL, ESMO, AASLD, the British, and Italian societies^[1,6,35-37] show growing alignment with the methodological principles of MTH, signalling a wider shift away from inflexible algorithmic models such as the prescriptive part of the BCLC framework [Table 2 and Figure 2]. This alignment underscores both the relevance and potential of MTH as a practical, scalable, and adaptable reference for real-world clinical practice.

By providing the conceptual framework for the Special Issue, MTH not only shapes the logic of subsequent contributions but also guarantees that the evolving science of HCC management is rooted in a coherent, multidisciplinary, and future-oriented strategy.

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All authors have reviewed and approved the final version of the manuscript.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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