Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept

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Advances in the surgical and systemic therapeutic landscape of hepatocellular carcinoma have increased the complexity of patient management. A dynamic adaptation of the available staging-based algorithms is required to allow flexible therapeutic allocation. In particular, real-world hepatocellular carcinoma management increasingly relies on factors independent of oncological staging, including patients' frailty, comorbid burden, critical tumour location, multiple liver functional parameters, and specific technical contraindications impacting the delivery of treatment and resource availability. In this Policy Review we critically appraise how treatment allocation strictly based on pretreatment staging features has shifted towards a more personalised treatment approach, in which expert tumour boards assume a central role. We propose an evidence-based framework for hepatocellular carcinoma treatment based on the novel concept of multiparametric therapeutic hierarchy, in which different therapeutic options are ordered according to their survival benefit (ie, from surgery to systemic therapy). Moreover, we introduce the concept of converse therapeutic hierarchy, in which therapies are ordered according to their conversion abilities or adjuvant abilities (ie, from systemic therapy to surgery).

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Introduction

Hepatocellular carcinoma is a challenging malignancy of global importance, characterised by clinical and biological heterogeneity, and is often associated with a poor prognosis.[1] Prediction of outcome and choice of treatment strategy is particularly complex in patients with hepatocellular carcinoma due to the prognostic impact of underlying liver disease and the high prevalence of clinical frailty.[2]

Over the past 20 years, treatments for hepatocellular carcinoma have remarkably improved, which has, in turn, increased the complexity of disease management. The improvements affect all tumour stages, including the implementation of transplant benefit criteria, adoption of mini-invasive surgical techniques, advancements in intra-arterial treatments, and the development of novel systemic therapies in unresectable or advanced tumours, providing survival benefits as first-line, second-line, or third-line therapies.[3–6] Moreover, preliminary results from studies of the involvement of systemic therapies in conversion[7] or adjuvant strategies[8] suggest they will probably increase the feasibility and effectiveness of radical treatments in the future.

The Barcelona Clinic Liver Cancer (BCLC) system improved hepatocellular carcinoma care in the late 1990s by standardising treatment allocation according to an evidence-based method.[9] The dynamic changes in hepatocellular carcinoma care that have occurred since this standardisation have promoted substantial refinements of the original framework, considering the wide prognostic heterogeneity of patients presenting in each stage.[2,10] Despite this standardisation and refinement, several therapeutic frameworks for hepatocellular carcinoma management have been proposed worldwide over the past 20 years in answer to dissonance between guidelines and real-world decision making.

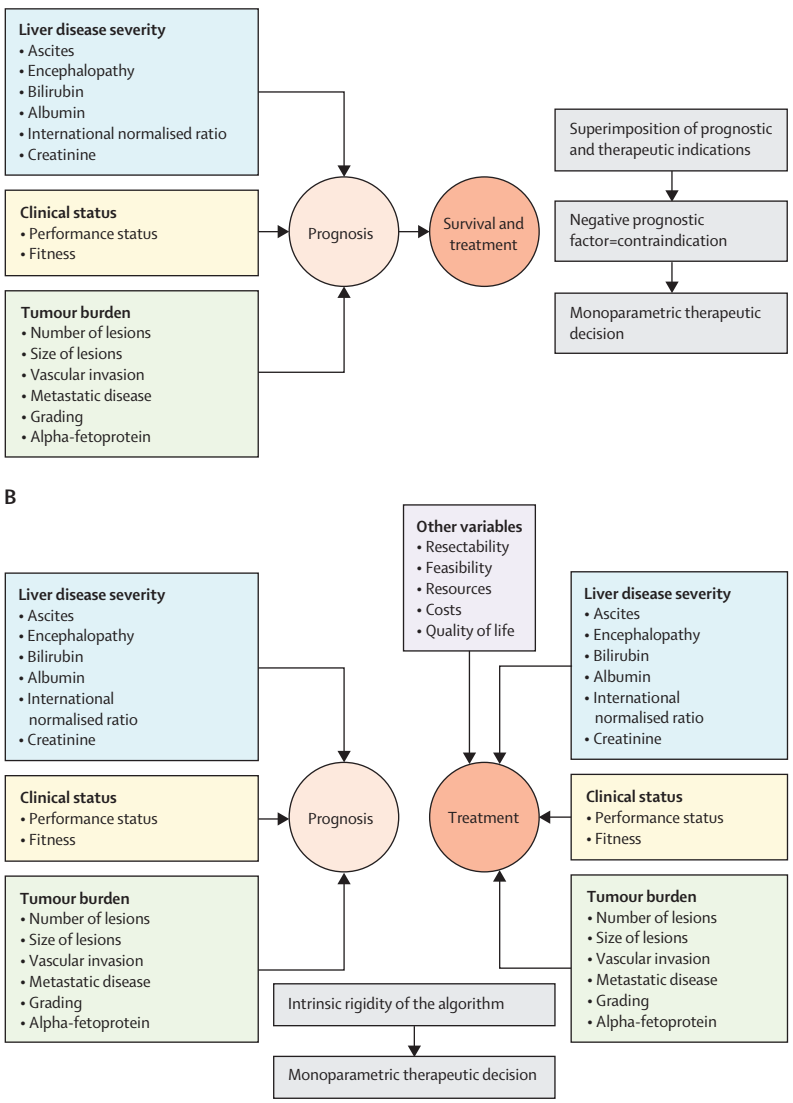
The first aim of this Policy Review is to provide a critical revision of the literature surrounding the evolution and adaptation of conceptual approaches to hepatocellular carcinoma management. The conceptual approach dominated by stage hierarchy—linking each stage of the disease to a specific treatment—has become the mainstay for managing hepatocellular carcinoma, particularly in the USA and Europe.[10]

An alternative approach to stage hierarchy is to consider the treatment decision to be hierarchically dictated by the effectiveness of each therapy, either fully or partly independent from the tumour stage. This therapeutic hierarchy approach has been historically endorsed by Asia-Pacific and Japanese treatment algorithms[11,12] and the recent Italian multisociety guidelines.[13]

Independent from the adopted stage or therapeutic hierarchy framework, in the past 10 years, support has grown for treatment deriving from decisions taken by an expert multidisciplinary tumour board, who are able to adopt a personalised therapeutic approach tailored to the characteristics of each patient.[3,13–16] The complex management of hepatocellular carcinoma, both in the early and advanced stages, is recognised to require multidisciplinary expertise due to advances in the diagnosis, staging, and treatment options.

A patient-centred approach requires a case-by-case evaluation of several clinical and psychosocial factors, including comorbid conditions, patient insight, preferences, and the impact of treatment on the patients' quality of life.

Given this background, the second aim of this Policy Review is to provide a novel framework for a therapeutic approach tailored to patient status, tumour characteristics, liver function, and the technical feasibility of each treatment. The fundamental idea of this proposal is to



create a clinically useful tool to support the decision-making process in hepatocellular carcinoma care delivered by an expert multidisciplinary tumour board, overcoming the use of rigid therapeutic algorithms.

The original concepts of stage and therapeutic hierarchy

The paradigm of the stage hierarchy approach is represented by the BCLC classification.[17,18] In the original BCLC definition,[17] treatment is considered an outcome variable similar to survival (figure 1A). For example, liver disease severity, patient clinical status, and tumour burden are simultaneously used to establish prognostic stage and treatment choice, meaning stages or substages dictate treatment allocation. Therefore, prognostic classification coincides with the treatment algorithm.

Since 2015, other proposals from Hong Kong, China, and South Korea have incorporated a stage hierarchy approach linking hepatocellular carcinoma stages to specific therapeutic indications.[19–21] The BCLC system has globally promoted and diffused an evidence-based approach tailored to managing patients with hepatocellular carcinoma. The simplicity of the algorithm, which has undergone several iterations and updates, is appealing to clinicians, potentially allowing the formulation of a treatment decision without the support of a multidisciplinary evaluation of the case.[9]

Other key features of the BCLC algorithm are the ability to predict the history of untreated hepatocellular carcinoma and the potential to stratify patients for clinical trials.[22,23] Following robust external validation in different geographical areas, the European and North American hepatology scientific societies recommended the BCLC staging and its updated versions, which became the benchmark of the evidence-based combined prognostic–therapeutic algorithms for hepatocellular carcinoma management.

The second concept for treatment allocation of patients with hepatocellular carcinoma is the treatment hierarchy approach, which has been developed over the past 20 years in parallel with the stage hierarchy approach. Historically, this paradigm refers to the independence of treatment from prognostic classification (figure 1B). This total or partial independence from specific stages is typical of most treatment algorithms for solid cancers.[24–26] For hepatocellular carcinoma, stage-independent treatment algorithms have been proposed by the Asia-Pacific and

Figure 1: **Original definitions of stage hierarchy, treatment hierarchy, and ordinal therapeutic hierarchy**
(A) In the stage hierarchy definition, treatment is considered an outcome variable similar to survival. (B) In the treatment hierarchy definition, staging or prognostic systems and treatment allocation or algorithm are independent; staging can help to inform, but not dictate, treatment allocation. (C) In the ordinal therapeutic hierarchy, treatment is used as an independent predictor variable and an ordinal variable (ie, in a hierarchical order of therapeutic options).

Japanese guidelines.[11,12] The Japanese Integrated Staging score is used for the prognostic assessment of patients with hepatocellular carcinoma, and does not guide the algorithm used for treatment allocation.[12] This segregation between prognostic prediction and treatment allocation allows the introduction of variables, such as resectability,[11,12] not necessarily included in a staging system (figure 1B).

Variants of the stage and therapeutic hierarchy concepts

The intrinsic nature of the stage hierarchy approach, and the algorithm structure of both the stage and treatment hierarchy strategies (figures 1A, 1B), have been accused of giving rigidity to the decisional framework, limiting its use and real-world applicability.[27,28] Variables included in the algorithms risk being intrinsically used as monoparametric contraindications to a specific treatment, leading to the potential exclusion of relevant proportions of patients from clinically effective therapies.[29,30] Moreover, the original therapeutic hierarchy algorithms are affected by geographical and cultural differences, such as the scarcity of deceased liver donors[11] or different approaches to neoplastic portal thrombosis between specific groups of countries: western countries (Europe and the USA in particular) and eastern countries (China, Japan, and South Korea in particular).[31]

Some variants of the original frameworks have been proposed to increase the plasticity of the stage and therapeutic hierarchy approaches, and to adapt them to advances in treatment options for hepatocellular carcinoma.

Stage hierarchy variants

In a large multicentre study,[28] only a third of patients undergoing liver resection worldwide met the original BCLC criteria. Similarly, in a single centre observational study in Italy,[32] hepatocellular carcinoma treatment needed to adhere to guidelines in almost half of enrolled patients with intermediate and advanced-stage hepatocellular carcinoma. Non-adherence to the stage-specific recommended treatment was also found in a study of a large South Korean cohort,[33] in which the Hong Kong algorithm was used.[19]

More flexibility to the stage hierarchy approach has been introduced into international guidelines over the past few years, particularly those by the European Association for the Study of the Liver,[2] the American Association for the Study of Liver Diseases,[34] and the 2022 updated version of the BCLC.[18] Variations in stage hierarchy include treatment stage migration, treatment stage alternative, and clinical decision-making strategies.[1]

The treatment stage migration approach was initially defined as the possibility of offering the patient the next most suitable treatment option within the same stage, or the one indicated for the subsequent (more advanced) stage, when the first option is contraindicated.[10] Not only is a horizontal left-to-right treatment stage migration suggested (ie, if ablation or surgical resection are contraindicated as first-line therapy in patients with BCLC A then intra-arterial treatment should be considered), but also a sequential left-to-right treatment stage migration, which is defined as a shift to the next most suitable option at the time of restaging following an unsatisfactory response to the first-line therapy.[10,35,36] The European Association for the Study of the Liver guidelines introduced an important innovation in 2018—namely, the allowance for a restricted right-to-left treatment stage migration in highly selected patients, with parameters close to the thresholds defining the adjacent, less advanced stage.[2] An example of evidence-based right-to-left sequential migration is represented by the possibility of offering liver transplants to selected patients with BCLC B within validated, extended criteria.[37–39]

Another variant of the stage hierarchy approach is the treatment stage alternative approach.[1] This model proposes different therapeutic solutions for each stage of the disease, where initial options (standard of care) are presented alongside alternative solutions. The first refinement of the BCLC scheme according to the treatment stage alternative policy, together with a substratification of the intermediate stage, was done by a group of experts in 2012.[40] The American Association for the Study of Liver Diseases and the European Society of Medical Oncology have also proposed to give more flexibility to the BCLC scheme, by introducing a treatment stage alternative modification of the algorithm.[34,41]

Finally, a clinical decision-making variant of stage hierarchy was introduced in the 2022 BCLC update.[18] This variant is characterised by an innovative tumour board dedicated section, graphically represented as a second box placed below the main algorithm, in which the possibility of left-to-right treatment stage migration is evaluated.

Treatment hierarchy variants

The 2016 multisociety Italian guidelines[13] have proposed the treatment hierarchy battleship scheme (appendix p 2). This proposal recommends more first-choice and second-choice treatments based on tumour characteristics (vertical axis) or functional parameters (horizontal axis).

An evolution of the therapeutic hierarchy concept considers treatment as an independent ordinal prognostic variable and not only as an independent algorithm, as in the original definition (figure 1C). Namely, in the ordinal treatment hierarchy variant, the variable of treatment choice represents an ordinal variable with the following hierarchical order of decreasing efficacy: liver transplantation, liver resection, ablation, intra-arterial therapy, systemic therapy, and then best supportive care. This concept is supported by evidence that the treatment choice, from a statistical standpoint, maintains prognostic independence from the hepatocellular carcinoma stage

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See **Online** for appendix

and other variables in multivariable survival analyses (table 1, appendix p 3).[14,42–44] From a clinical standpoint, the survival benefit of the treatment maintains its hierarchical order within each tumour stage.[1,42] This concept is clinically evident in very early and early stages, where the recommendations are more granular even in stage hierarchy approaches (including surgical and ablative therapies as the standard of care; table 2, appendix p 4)[4,32,33] before considering less effective treatments, such as intra-arterial therapies or systemic therapies.

The ordinal therapeutic hierarchy strategy is particularly important in intermediate and advanced stages of hepatocellular carcinoma, when potentially curative therapies are usually excluded from stage hierarchy approaches. There is evidence that surgical treatments could offer an overall survival benefit compared with locoregional or systemic therapies in both intermediate[4,32,33,45–47] and advanced stages,[29,30,48–50] which is maintained after propensity score adjustment of baseline characteristics, or testified by randomised clinical trials (table 2, appendix p 4). Furthermore, from a clinical standpoint, the ordinal therapeutic hierarchy approach empowers clinicians to assess whether the most effective therapy is safely feasible regardless of the presenting tumour stage,[43,51] and, if contraindications exist, it allows complete flexibility by de-escalating the treatment choice according to decreasing efficacy until viable treatment is identified[1,42] (figure 1C). The ordinal therapeutic hierarchy concept can not only be applied in first-line treatment decisions, but also at each restaging evaluation of the patient.[43]

Finally, we define a novel therapeutic hierarchy variant: the converse therapeutic hierarchy.

This term does not refer to the survival benefit of hepatocellular carcinoma treatments—as the ordinal therapeutic hierarchy does—but rather to the ability of systemic and locoregional therapies to increase the feasibility and effectiveness of radical therapies, potentially making surgery feasible in previously non-surgical patients and allowing a treatment scale-up. Although clinical trials in this setting are still required, some observational studies suggest that a triple combination approach, including locoregional therapy, lenvatinib, and immunotherapy, can reach a conversion rate to liver resection of about 40% in patients with intermediate, initially unresectable hepatocellular carcinoma.[7] From this perspective, the hierarchy of treatments is inverted, since systemic therapies have the potential of improving the biology of aggressive tumours,[47] and therefore increasing the indications (feasibility) to radical therapies.

Preliminary data published in 2023[8,52] concerning the IMbrave 050 trial suggest that novel systemic therapy combinations can also improve the effectiveness of radical therapies (adjuvant approach), significantly reducing the risk of post-treatment hepatocellular carcinoma recurrence, compared with active follow-up.

The new proposal: the multiparametric therapeutic hierarchy approach

Stage hierarchy and therapeutic hierarchy variants increase the adherence rate to the original algorithms, improving their clinical flexibility in the context of multidisciplinary tumour boards. However, both variants have some limitations. Stage hierarchy variants (ie, treatment stage migration, treatment stage alternative, and clinical decision making) still focus on a single therapy for each stage or substage. This initial therapy is identified as the standard of care or first-line option on the basis of the degree of evidence. However, the recommended treatment is often less effective than other potentially feasible options with greater survival benefits. For example, transarterial chemoembolisation has the most evidence (ie, a randomised clinical trial proving its efficacy) for the treatment of intermediate hepatocellular carcinoma,[41] but liver resection offers better survival for patients with resectable, intermediate hepatocellular carcinoma.[32,45,46] The three variants, therefore, maintain a stage hierarchy vulnerable to the

	Study design (n)	Survival outcome measure by therapy received (N; HR, 95% CI)							Comments
		No therapy	Liver transplantation	Resection	Ablation	Transarterial therapy	Sorafenib	Other	
Serper M et al (2017)[14]	Observational (3988)	1436; 1 (reference)	160; 0·18, 0·13–0·25	160; 0·31, 0·13–0·25	439; 0·50, 0·42–0·60	1755; 0·72, 0·65–0·80	1555; 1·70, 1·54–1·86	NA	Multivariable time varying Cox analysis including BCLC staging
Vitale et al (2019)[42]	Observational controlled with IPTW (4867)	1210; 1 (reference)	174; 0·19, 0·18–0·20	645; 0·40, 0·37–0·42	1546; 0·42, 0·40–0·44	1085; 0·58, 0·55–0·61	207; 0·92, 0·87–0·97	NA	Multivariable IPTW Cox analysis including Italian Liver Cancer staging
Vitale et al (2018)[43]	Observational (1196)	176; 6·30, 3·17–14·36	41; 1 (reference)	37; 2·10, 0·85–5·45	164; 2·93, 1·47–6·68	446; 3·66, 1·90–8·20	253; 3·57, 2·87–12·52	79; 5·70, 2·78–13·29	Multivariable Cox analysis including Italian Liver Cancer score performed at restaging before additional treatment decision
Kawaguchi et al (2021)[44]	Observational controlled with IPTW (43 904)	NA	NA	15 313; 46·2%, 44·0–48·3*	15 216; 33·4%, 31·1–35·7*	13 375; 27·4%, 25·0–29·8*	NA	NA	Multivariable IPTW Cox analysis including tumour burden.

HR=hazard ratio. NA=not applicable. BCLC=Barcelona Clinic liver cancer. IPTW=inverse probability of treatment weighting. *5-year survival (95% CI).

Table 1: **Studies supporting therapeutic hierarchy as independence of ordinal treatment variable from tumour staging (multivariable models)**

	Study design (n); country	Therapies and survival outcome measures by BCLC stage					Comments
		Very early	Early	Single >5 cm	Intermediate	Advanced	
Vitale et al (2015)[4]	Observational, Child-Pugh class A (1181); Italy	Resection 92 months, ablation or TACE 62 months*	Resection 72 months, ablation or TACE 50 months*	Resection 55 months, ablation or TACE 42 months*	Resection 52 months, ablation or TACE 41 months*	NA	Multivariate log-logistic parametric survival analysis including patient, liver function, and tumour-related variables, and using treatment as stratifying covariate
Kim et al (2016)[33]	Observational (3515); South Korea	Surgery or ablation 84%, TACE 64%; p<0·001†	Surgery or ablation 74%, TACE 44%; p<0·001†	NA	Surgery or ablation 53%, TACE 33%; p=0·003†	Surgery or TACE 22%, sorafenib 10%; p<0·001†	Univariable and multivariable Cox analyses
Sangiovanni et al (2018)[32]	Observational (370); Italy	NA	Surgery or ablation 5·0%, TACE 10·4%; p=0·004‡	NA	Surgery or ablation 8·6%, TACE 20·7%; p=0·029	Surgery or TACE 42·6%, sorafenib 59·0%; p=0·040	Univariable and multivariable Cox analyses
Pecorelli et al (2017)[45]	Observational with propensity score matching (485); Italy	NA	NA	NA	Curative surgery or curative ablation 45 months (HR 0·20, 95% CI 0·10–0·40), TACE 30 months (HR 0·41, 0·21–0·79), sorafenib 14 months (HR 0·80, 0·29–2·20), best supportive care 10 months (1 [ref])*	NA	Multivariable Cox analysis, propensity score matching
Yin et al (2014)[46]	Randomised clinical trial (173); China	NA	NA	NA	Resection 51·5% (HR 0·43, 95% CI 0·29–0·64), TACE 18·1% (1 [ref]); p<0·001§	NA	Log-Rank test, multivariable Cox analysis
Mazzaferro et al (2020)[47]	Randomised clinical trial (74); Italy	NA	NA	NA	Liver transplantation 77·5% (HR 0·32, 95% CI 0·11–0·92), non-transplant therapy 31·2% (1 [ref]); p=0·035†¶	NA	Log-Rank test, multivariable Cox analysis
Kokudo et al (2016)[29]	Observational with propensity score matching (2116); Japan	NA	NA	NA	NA	Liver resection 2·45 years, non-surgical therapy 1·57 years; p<0·001*‖	Propensity score matching and multivariable Cox analysis for the liver resection group
Kokudo et al (2017)[30]	Observational with propensity score matching (446); Japan	NA	NA	NA	NA	Liver resection 3·42 years, non-surgical therapy 1·81 years; p=0·023*·**	Propensity score matching and multivariable Cox analysis for the liver resection group
Mej et al (2020)[48]	Observational with propensity score matching (144); China	NA	NA	NA	NA	Liver resection 27·2 months, sorafenib 13·0 months; p<0·001*·††	Propensity score matching survival analysis
Govalan et al (2021)[49]	Observational with propensity score matching (264); USA	NA	NA	NA	NA	Liver resection 21·4 months, systemic therapy 8·1 months; p<0·001*·††	Propensity score matching and multivariable Cox analysis for the liver resection group
Famularo et al (2022)[50]	Observational with IPTW (478); Italy	NA	NA	NA	NA	Liver resection 55·9% (1 [ref]), sorafenib 12·8% (HR 4·44, 95% CI 3·19–6·15); p<0·001†	IPTW based creation of two pseudo-populations for survival curve comparison; IPTW multivariable cox analysis

BCLC=Barcelona Clinic Liver cancer. TACE=transarterial chemoembolisation. NA=not applicable. HR=hazard ratio. IPTW=inverse probability of treatment weighting. *Median survival. †5-year survival. ‡Mean mortality rate. §3-year survival. ¶Intermediate tumour responsive to downstaging. ‖Portal vein invasion. **Hepatic vein invasion. ††Vascular invasion.

Table 2: **Studies supporting therapeutic hierarchy as an ordinal therapeutic variable within tumour stages**

risk of undertreatment.[1] The complexity of the treatment hierarchy battleship variant (appendix p 2) makes this model difficult to adopt in clinical practice. By contrast, an unconditional application of the ordinal treatment hierarchy (figure 1C) strategy could promote over-treatment in some patients.

A crucial limitation of the stage and therapeutic hierarchy variants is the insufficient representation of key variables influencing the decision process in real-world hepatocellular carcinoma management, including patient frailty, presence of comorbidities, critical tumour location, and specific technical factors (eg, previous upper

abdominal surgery increases the technical complexity of liver transplantation and arterial anatomical variants increase the technical complexity of intra-arterial therapies) affecting the delivery of treatment and resource availability. As treating clinicians have become more aware of the sources of heterogeneity in hepatocellular carcinoma management, a consensus has been reached on the importance of personalised management in the context of an expert multidisciplinary tumour board.[3,4,15] Considering the clinical limits of available frameworks, and the pronounced change in hepatocellular carcinoma management, a shift in the framework of therapeutic approaches is needed, with tailoring to patient status, tumour characteristics, liver function, and the technical feasibility of each treatment.

On the basis of the above considerations, we propose a novel conceptual framework for the multidisciplinary management of patients with hepatocellular carcinoma (figure 2, appendix p 7). The new proposal is based on three concepts that are capable of working synergistically and compensating for their limits.

First, we have chosen the ordinal therapeutic hierarchy paradigm. In contrast to the other stage and therapeutic hierarchy variants, this paradigm offers the advantage of bringing the clinician's choice towards the most effective therapy and, if judged unfeasible, to proceed with alternative approaches ordered according to their proven efficacy. The new proposal facilitates clinicians to offer therapies that are known to confer the best survival benefit for the patient, to adapt treatment choices on an individual patient basis, and to respect the evidence in support of the efficacy of the chosen therapy.[1]

Second, a new multiparametric model has been proposed since only an expert multidisciplinary tumour board can consider all the variables (ie, clinical, technical, psychological, and social) influencing the treatment decision to adopt a personalised approach. On one hand, the multidisciplinary team evaluation can prevent the risk of overtreatment inherent in the therapeutic hierarchy approach. On the other hand, the ordinal therapeutic hierarchy, which limits clinicians to adopt the most effective therapy feasible, can avoid the risk of undertreatment.

Third, although evidence from clinical trials is scarce, the converse therapeutic hierarchy concept has been added to the novel framework because it has the potential to change the feasibility (conversion approach) and effectiveness (adjuvant approach) of hepatocellular carcinoma radical therapies.

To overcome the lack of flexibility of previous frameworks, our proposal is not embedded within a specific algorithm, but is based on a flexible multiparametric decisional framework (figure 2, appendix p 7). The new proposal attempts to reproduce the therapeutic decision-making process typical of multidisciplinary meetings composed of highly specialised medical professionals. While recognising staging characteristics as important overarching features of the decision-making approach, the multiparametric model adopts practical clinical reasoning, starting from treatment feasibility in the individual patient rather than from the tumour stage at presentation. In this approach, the feasibility of all treatments is evaluated systematically in a hierarchical order in the vertical axis (ie, liver transplantation, surgical resection, ablation, intra-arterial therapies, systemic therapy, and best supportive care) with the aim to match each patient with the optimal therapy, and avoid the risks of overtreatment and undertreatment. For each treatment, any relative or absolute contraindications are considered, and if the risk–benefit ratio is not acceptable, the next therapeutic step is considered. From this perspective, the new proposal considers, in the horizontal axis, all variables involved in this multiparametric evaluation and avoids leaving out any important ones. This scheme should be applied in both first-line treatment decisions, and in each restaging evaluation and decision making.[1,43]

Vertical axis: therapeutic hierarchy

Ordinal therapeutic hierarchy is represented in the left vertical axis, because much evidence supports this concept (tables 1, 2, appendix pp 3–6). Unlike other proposals,[10,37] the scheme considers the possibility of adopting laparoscopic ablation before dropping the decision to intra-arterial therapies, according to evidence showing that improved survival can be achieved with laparoscopic ablation.[53,54] The concept of converse therapeutic hierarchy is represented in the right vertical axis. We describe the relative contraindications and absolute contraindications of each therapeutic strategy in the appendix (pp 8–18).

Horizontal axis: multiparametric expert decision

The new proposal introduces the unfit variable that is already used for managing other solid cancers.[25] Patients are assessed as either fit or unfit, according to general conditions such as age, frailty, and comorbidities rather than cancer-related symptoms. This parameter avoids the misleading interpretation of the variable performance status when used to assess general patient conditions. Comorbidities are included in this proposal, because specific comorbidities (eg, cardiovascular disease, chronic obstructive pulmonary disease, obesity, and diabetes) might represent relative contraindications to some anti-hepatocellular carcinoma therapies.[55,56] To measure the effect of comorbidities, the Charlson comorbidity index[57] was correlated with the post-treatment outcome in patients with hepatocellular carcinoma.[58]

Physical frailty describes a biological status characterised by a high clinical vulnerability to stressors.[59] It originates from geriatric medicine, and several tests measure frailty,[59]

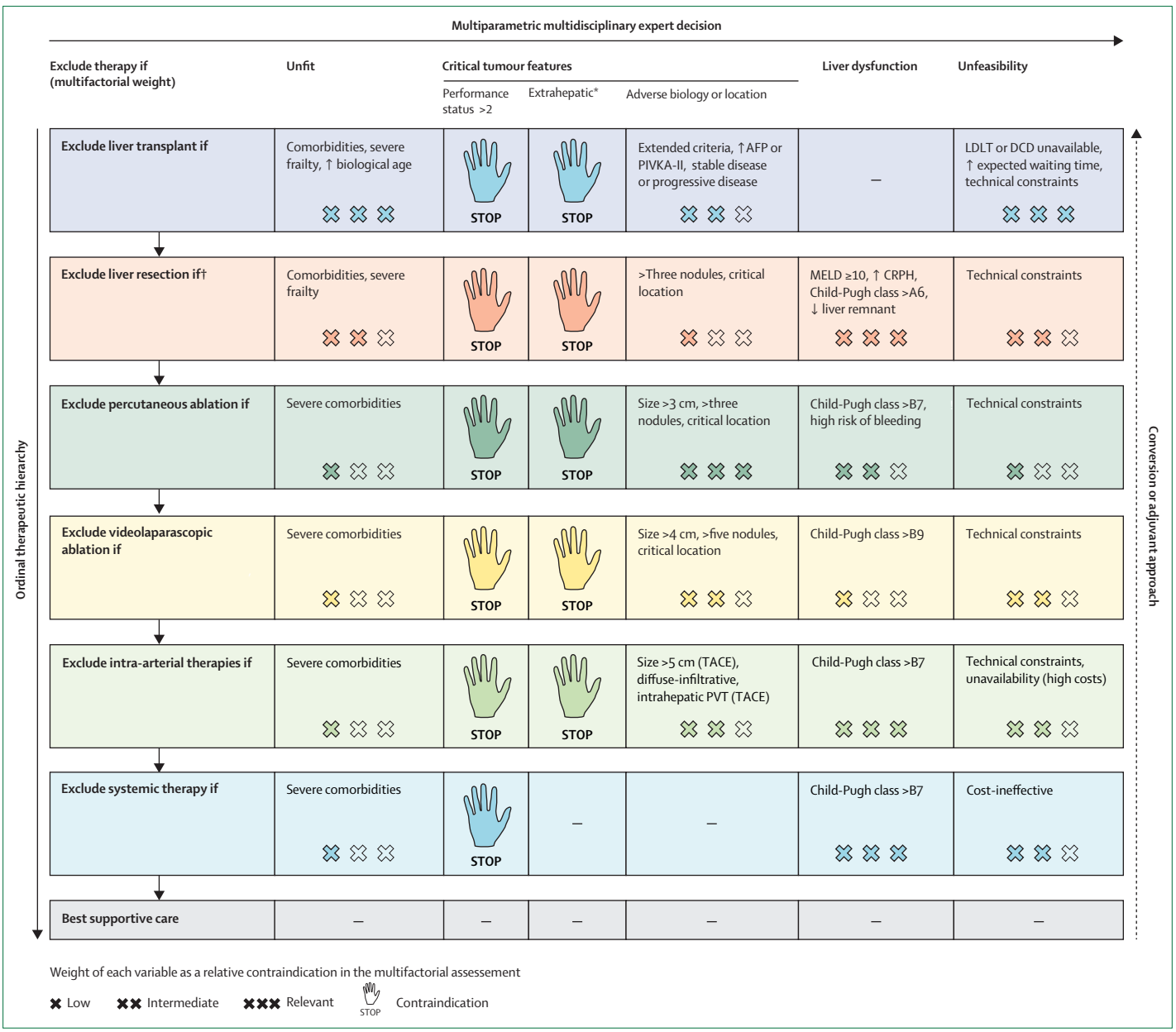

Figure 2: **Multiparametric therapeutic hierarchy**

The concept of converse therapeutic hierarchy is represented with a dashed arrow, since the evidence supporting this concept is still weak. AFP=alpha-fetoprotein. PIVKA-II=Protein Induced by Vitamin-K Absence-II. LDLT=living donor liver transplantation. DCD=donor after circulatory death. MELD=model for end-stage liver disease. CRPH=clinically relevant portal hypertension. TACE=transarterial chemoembolisation. PVT=portal vein thrombosis. *Extrahepatic metastases, invasion of the main trunk of the portal vein or inferior vena cava. †Mini-invasive approach offers a prognostic advantage (decreased risk of postoperative liver failure), and decreases the impact of liver dysfunction by one cross.

including the Fried frailty index.[60] In patients with cirrhosis, sarcopenia is a morphological correlate of frailty, and there is evidence that patients with sarcopenia have poorer outcomes after major surgery.[61]

Critical tumour features is another essential parameter not usually included in treatment algorithms for hepatocellular carcinoma. As in the recent BCLC update,[18] we highlight that performance status assessment is only an expression of tumour-related symptoms, not of baseline symptoms already present before cancer diagnosis or pre-existing comorbidities. From this perspective, it is important to distinguish patient unfitness from performance status as a surrogate of tumour aggressiveness, independently establishing the feasibility of available therapies.

Extrahepatic hepatocellular carcinoma refers to the presence of extrahepatic metastases or invasion of the main trunk of caval or portal veins. It is important to

distinguish extrahepatic from intrahepatic macrovascular invasion, because the latter can be susceptible to surgical or locoregional therapies.[50]

Aggressive hepatocellular carcinoma biology is correctly described when the tumour burden and tumoural biomarkers, such as alpha-fetoprotein and Protein Induced by Vitamin-K Absence-II (PIVKA-II) concentrations, stability or progression after locoregional therapies, and positive PET scans are considered. These biological variables are in the validated extended criteria for liver transplant.[39]

PIVKA-II is infrequently used as a tumour marker in Europe and the USA.[62] Several studies in China, Japan, and South Korea have shown its potential role in the diagnosis and prognosis of hepatocellular carcinoma, in both curative and palliative settings.[63–65] The ability to predict tumour recurrence of PIVKA-II from alpha-fetoprotein has been shown after liver resection[64] and liver transplantation.[63] The Model of Recurrence After Living donor liver transplantation score was developed following a South Korean study involving 566 recipients, in which the product of concentrations of the two biomarkers PIVKA-II and alpha-fetoprotein allowed the identification of patients at high risk of post-transplant recurrence, independently of tumour morphology.[66] The combination of alpha-fetoprotein and PIVKA-II is, therefore, a reliable indicator intended to improve the evaluation of patients' conditions.

The location of hepatocellular carcinoma is another crucial parameter for treatment decisions.[67] A superficial or deep location is a mainstay for deciding between surgery or ablation. Similarly, a subcapsular position close to the abdominal viscera can be a contraindication to percutaneous ablation, supporting the decision to adopt a laparoscopic approach.[67] An evaluation of liver dysfunction is usually included in all algorithms for hepatocellular carcinoma treatment. However, this parameter is often restricted to the definition of the Child-Pugh class.[68] Therefore, assessing liver functional reserve at baseline and during follow-up[3,63] is complex and multifaceted. Other scores are frequently used to refine the information from the Child-Pugh class, such as the model for end-stage liver disease, model for end-stage liver disease-sodium score, albumin-bilirubin grade, indocyanine green test, and liver stiffness,[68–73] as mentioned by the updated BCLC algorithm.[18]

Causes of underlying liver disease can have an impact on the management of hepatocellular carcinoma, and adequate treatment of causal factors (ie, antiviral treatment in patients with hepatitis B virus and hepatitis C virus-related hepatocellular carcinoma) might reduce the risk of hepatic decompensation, leading to further treatment and improved survival rates.[74–76] A direct measurement of portal hypertension or a careful evaluation of indirect signs of clinically significant portal hypertension is essential to evaluate the patient's prognosis irrespective of treatment,[77] postoperative risk, and suitability for any treatment, including systemic therapy. Similarly, the calculation of remnant liver volume and the possibility of adopting a mini-invasive approach (laparoscopic or robotic) are fundamental parameters to consider in the resectability multiparametric evaluation process.[78]

Lastly, the term unfeasibility considers specific contraindications for each potential therapeutic choice and their potential effect is visually graded with crosses (figure 2, appendix p 7. The feasibility includes both technical and logistic issues. Each treatment can have specific technical constraints (stenotic coeliac arterial trunk, biliary disease, previous laparotomic surgery, etc) that only experienced specialists can overcome. Logistical issues include the adequate expertise of the specialists performing the procedures (ie, specialist curriculum and hospital case volume), and an adequate and complete team of experts to manage the patient during the treatment and peritreatment period (hospital requirements). Moreover, therapeutic resources are geographically variable—[79]for example, the availability of liver grafts from deceased donors. Waiting list size, blood group type, and the availability of deceased or living donors can influence the decision to select transplantation as the therapeutic solution for a patient.[80]

Search strategy and selection criteria

To describe the evolution and adaptation of conceptual approaches to hepatocellular carcinoma management and to develop the concept of multiparametric therapeutic hierarchy, we did a critical review of the literature on PubMed, MEDLINE, Embase, and Google Scholar from Jan 1, 2000, to Feb 28, 2023, without language restrictions. The following terms were used: "hepatocellular carcinoma", "HCC", "liver cancer", and "primary liver cancer", either individually or in combination with the terms "liver transplantation", "liver resection", "liver surgery", "locoregional treatment", "ablation", "radiofrequency ablation", "RFA", "microwave ablation", "MWA", "intra-arterial therapies", "TACE", "hepatic arterial infusion chemotherapy", "HAIC", "radioembolization", "TARE", "systemic therapy", "tyrosine kinase inhibitor", "immune checkpoint inhibitor", "palliative treatment", "best supportive care", "frailty", "performance status", "extrahepatic spread", "liver function", "tumor biology", and "tumor histology". Abstracts, case reports, letters, editorials, and non-English language articles were excluded, and priority was given to systematic reviews, meta-analyses, and original articles. Articles were also identified through searches of the authors' files. The reference list for assessment was generated based on relevance to the scope of this Policy Review.

Conclusions

Expert multidisciplinary tumour board evaluation is essential for the modern and effective management of patients with hepatocellular carcinoma. Although adaptive modifications of the stage and therapeutic hierarchy approach increase the adherence rate to the original algorithms and improve their clinical flexibility, they still carry the risk of overtreatment or undertreatment. This Policy Review addresses how the stage and algorithm paradigm can be safely and effectively implemented by broader and more flexible treatment selection criteria

that incorporate variables independent of oncological staging. The proposed multiparametric model draws strength from clinical guidelines and standard staging systems, rather than substituting them. It simultaneously attempts to offer a therapeutic allocation scheme more adherent to the reasoning of a multidisciplinary tumour board composed of highly specialised medical professionals.

Therapeutic allocation driven by the proposed multiparametric model begins from treatment feasibility in the individual patient, rather than from the tumour stage at presentation. It follows a clear and modern hierarchy of treatments stratified according to their potential evidence-based survival benefit. Our scheme is also open to the potential of locoregional and mainly systemic therapies as conversion or adjuvant therapies, introducing the concept of converse therapeutic hierarchy. Although our proposal does not intend to substitute current staging algorithms, the multiparametric model presented might be a valuable paradigm to optimise personalised anticancer treatment for patients with hepatocellular carcinoma.

Contributors

AV conceptualised and originally designed the Policy Review. AV and UC originally developed the concept of therapeutic hierarchy. UC conceptualised and graphically designed the novel framework (figure 2). AV, GC, FT, and UC contributed substantially to the Policy Review's concept or design. AV, GC, MI, LV, FRP, QL, AC-G, and CC searched the literature. AV, GC, MI, and UC wrote the Policy Review. FT and UC revised the Policy Review critically for important intellectual content. All authors independently analysed and selected the collected studies from the literature review, drafted the Policy Review section that pertained to their scientific and clinical expertise, and reviewed and approved the final version of the manuscript. All authors analysed policies and provided critical feedback. All authors contributed equally to this Policy Review.

Declaration of interests

GC declares consulting fees from Bayer, Roche, Ipsen, Merck Sharp & Dohme, Eisai, and AstraZeneca. MI declares consulting fees and honoraria for lectures from Bayer, Bristol Myers Squibb, Gilead Sciences, Roche, Ipsen, Merck Sharp & Dohme, and Eisai. DJP declares grants from Bristol Myers Squibb, Merck Sharp & Dohme, and GlaxoSmithKline; consulting fees from Mina Therapeutics, Eisai, Roche, Avamune, DaVolterra, Mursla, H3B, Ipsen, Exact Sciences, and AstraZeneca; payment for lectures from Roche, Bristol Myers Squibb, and Eisai; participation on advisory boards from Mina Therapeutics, Eisai, Roche, Avamune, DaVolterra, Mursla, H3B, Ipsen, LIfT Biosciences, Exact Sciences, and AstraZeneca. CC declares advisory board and speaker fees from Eisai, Merck Sharp & Dohme, and Ipsen. GG declares honoraria from Roche and Eisai. LC declares consulting fees from AstraZeneca, Biomedical, GEM, and Terumo; and payment for lectures from Angiodynamics, AstraZeneca, Boston, Cascination, Terumo, Varian, and Esaote. EGG declares honoraria for lectures from Eisai, Merck Sharp & Dohme, Roche, and AstraZeneca. FF declares honoraria from Roche and Eisai. FT declares research funding from Roche, AbbVie, Merck Sharp & Dohme, and Bayer; consulting fees and advisory boards from Roche, AstraZeneca, Eisai, and Bayer. All other authors declare no competing interests.

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