

EVENTO CONGIUNTO SICOP - AICEP

LIVER SURGERY **OPEN CHALLENGES** AND FUTURE PERSPECTIVES

CASTELNUOVO DEL GARDA

Presidenti: Dr. A. Giardino - Prof. L. De Carlis

28 NOVEMBRE
2025



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UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Multiparametric and Converse Therapeutic hierarchy in HCC

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Multiparametric and Converse Therapeutic Hierarchy in HCC

- From pre-Ptolemaic to Ptolemaic era



From pre-Ptolemaic to Ptolemaic era

HCC 1998: hic sunt leones!



In the late 1990s, no evidence existed supporting transarterial or systemic therapies as treatments for patients with HCC, and only three therapeutic options were known to confer survival benefit: liver transplantation, hepatic resection, and percutaneous ethanol injection

Trevisani F, Vitale A ... Cillo U. J Hepatol 2024

BCLC 1999



Journal of Hepatology 35 (2001) 421–430

Special article

Clinical Management of Hepatocellular Carcinoma. Conclusions of the Barcelona-2000 EASL Conference

Jordi Bruix*, Morris Sherman, Josep M. Llovet, Michel Beaugrand, Riccardo Lencioni, Andrew K. Burroughs, Erik Christensen, Luigi Pagliaro, Massimo Colombo, Juan Rodés, for the EASL Panel of Experts on HCC

Organizing Committee of the Conference: Henri Bismuth, Luigi Bolondi, Jordi Bruix and Daniel Shouval

Journal of
Hepatology

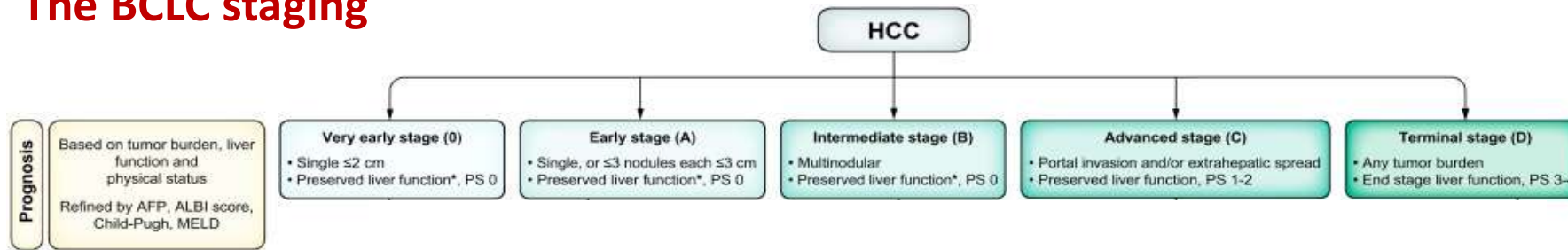
www.elsevier.com/locate/jhep

There are four main factors affecting prognosis:

- (a) the stage ... of the tumor;**
- (b) the general health of the patient;**
- (c) the liver function of the patient;**
- (d) the specific intervention.**

From pre-Ptolemaic to Ptolemaic era

The BCLC staging



Reig M, et al. J Hepatol 2022.

Singal AG, et al. Hepatology 2023.

Merits of the BCLC staging

1. Evidence-based approach
2. Comprehensive vision (patient, tumor, liver function)
3. Prognostic role of Treatment
4. Prognostic accuracy (stage stratification)
5. Simplicity (for clinicians and patients)
6. International consensus (guidelines)
7. Comparision of results (RCT design)

Trevisani F, Vitale A ... Cillo U. J Hepatol 2024

Multiparametric and Converse Therapeutic Hierarchy in HCC



- From pre-Ptolemaic to Ptolemaic era

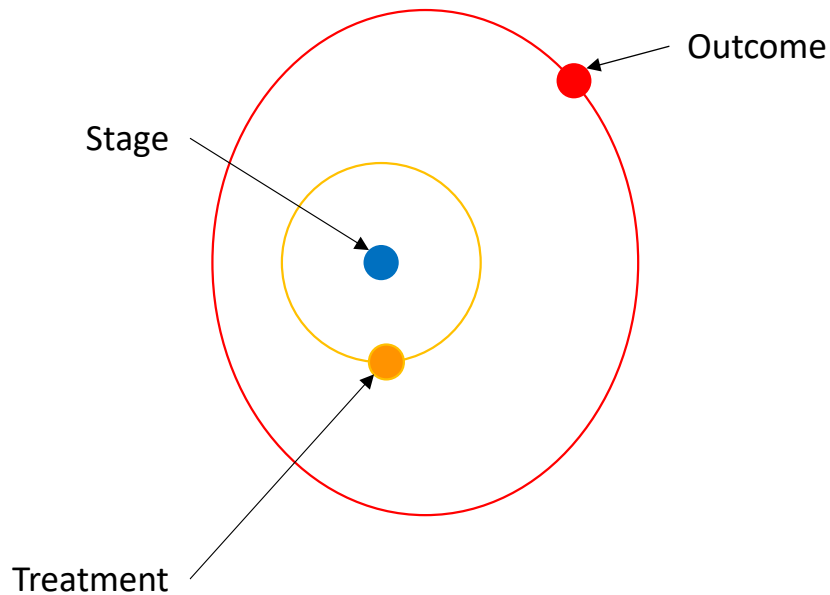
Merits of Stage Hierarchy

- The Ptolemaic System

The Ptolemaic System (stage hierarchy)

BCLC algorithm boundaries

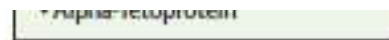
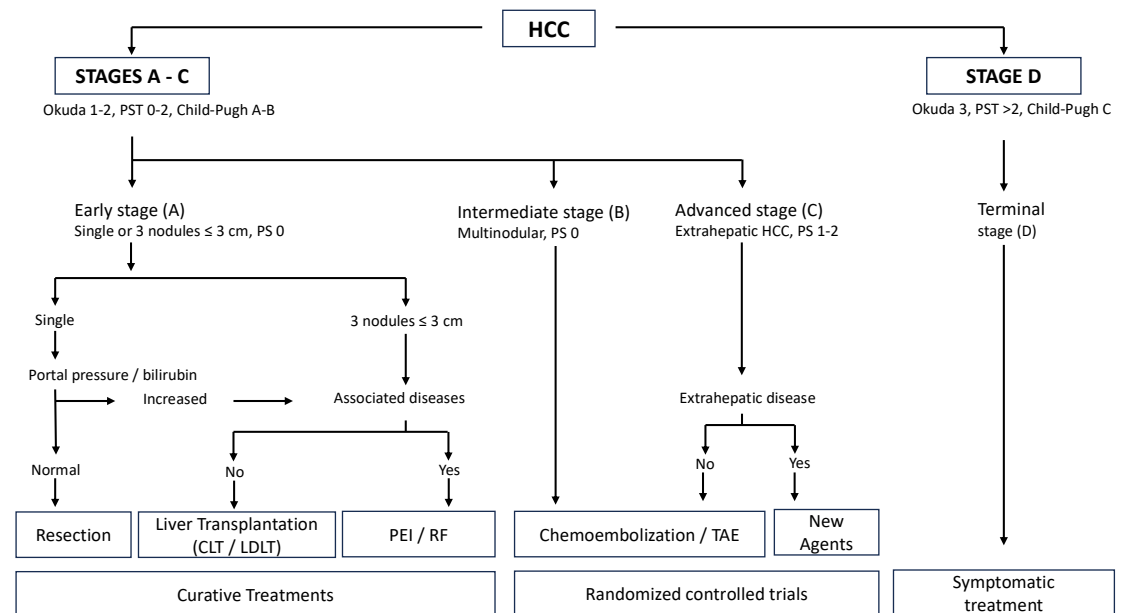
STAGE HIERARCHY



Ptolemaic System

STAGE HIERARCHY DEFINITION

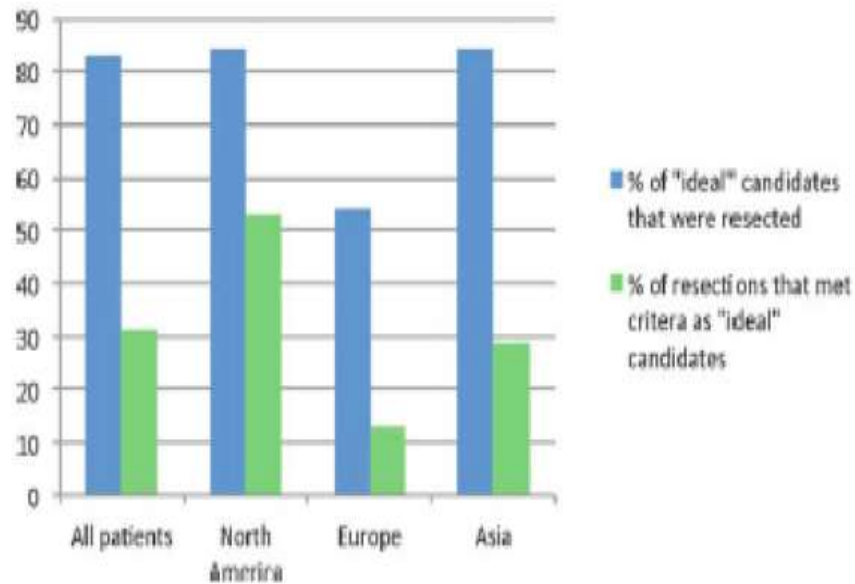
Treatment is considered
an outcome variable



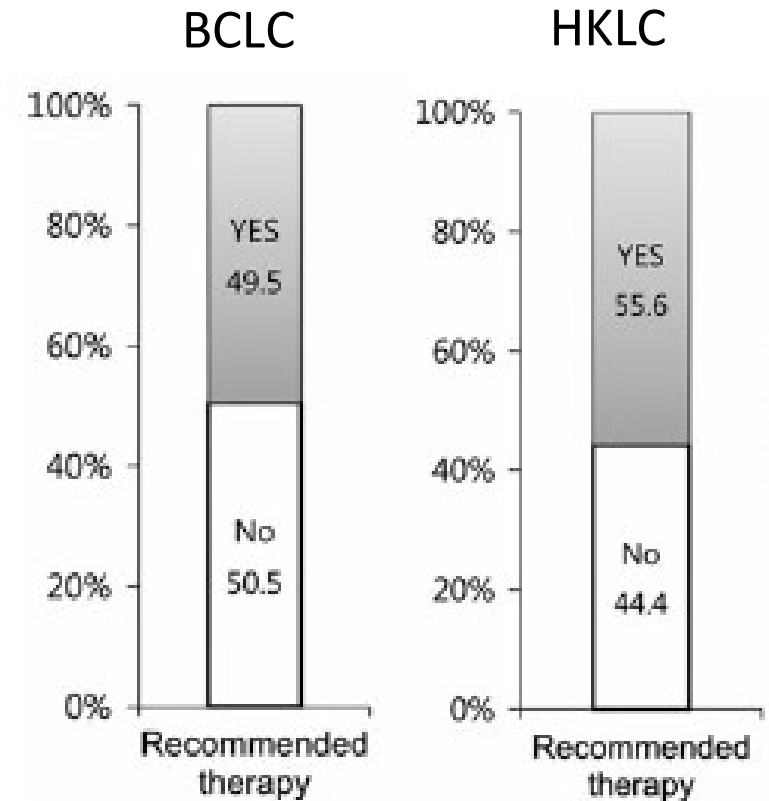
The Ptolemaic System (stage hierarchy)

BCLC algorithm boundaries

BCLC has been accused of “rigidity”, which would limit its utility in real life.



NON ADHERENCE



The Ptolemaic System (stage hierarchy)

BCLC algorithm boundaries

UNDER-TREATMENT

Lancet Oncol 2023; 24: e312-22

Policy Review

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

Alessandro Vitale, Giuseppe Cabibbo, Massimo Iavarone, Luca Viganò, David J Pinato, Francesca Romana Ponziani, Quirino Lai, Andrea Casadei-Gardini, Ciro Celsa, Giovanni Galati, Martina Gambato, Laura Crocetti, Matteo Renzulli, Edoardo G Giannini, Fabio Farinati, Franco Trevisani, Umberto Cillo, on behalf of the HCC Special Interest Group of the Italian Association for the Study of the Liver*



Study design (n)	Survival outcome measure by therapy received (N; HR, 95% CI)						
	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
Vitale et al (2019) ⁴¹	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
Vitale et al (2018) ⁴²	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
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

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)

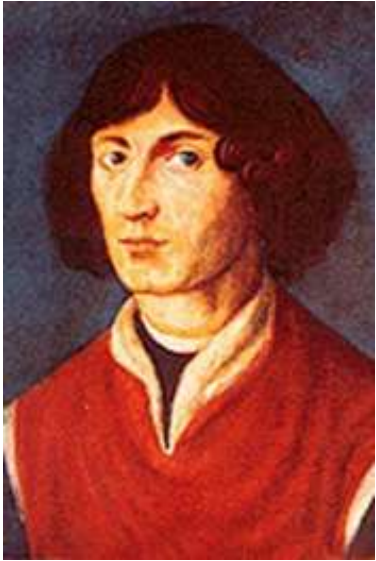
Study design (n); country	Therapies and survival outcome measures by BCLC stage					Comments
	Very early	Early	Single >5 cm	Intermediate	Advanced	
Vitale et al (2015) ⁴	Observational, Child-Pugh class A (1181); Italy	Resection 92 months, ablation or TACE 62 months*	Resection 72 months, ablation or TACE 50 months*	Resection 55 months, ablation or TACE 42 months*	Resection 52 months, ablation or TACE 41 months*	NA
Kim et al (2016) ⁴⁴	Observational (3525); 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†
Sangiovanni et al (2018) ⁴⁵	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
Pecorelli et al (2017) ⁴⁶	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
Yin et al (2014) ⁴⁷	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<0.0015	NA
Mazzaferro et al (2009) ⁴⁸	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
Kokudo et al (2016) ⁴⁹	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**‡
Kokudo et al (2017) ⁵⁰	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***
Mej et al (2020) ⁵¹	Observational with propensity score matching (144); China	NA	NA	NA	NA	Liver resection 27.2 months, sorafenib 13.0 months; p<0.001*††
Govaan et al (2021) ⁵²	Observational with propensity score matching (264); USA	NA	NA	NA	NA	Liver resection 21.4 months, systemic therapy 8.3 months; p<0.001*††
Famularo et al (2022) ⁵³	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

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 response to downstaging. ††Portal vein invasion. ***Hepatic vein invasion. †††Vascular invasion.

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

Vitale A, Cabibbo G, et al, Lancet Oncol 2023; 24: e312–22

Multiparametric and Converse Therapeutic Hierarchy in HCC



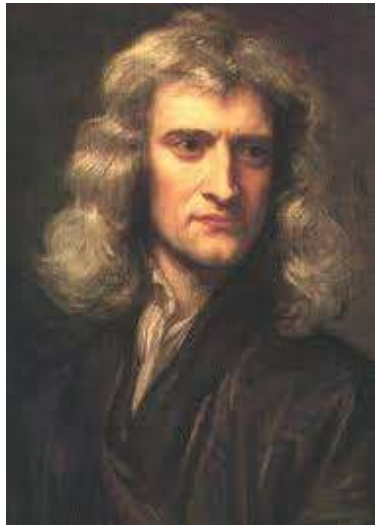
- From pre-Ptolemaic to Ptolemaic era

Merits of Stage Hierarchy

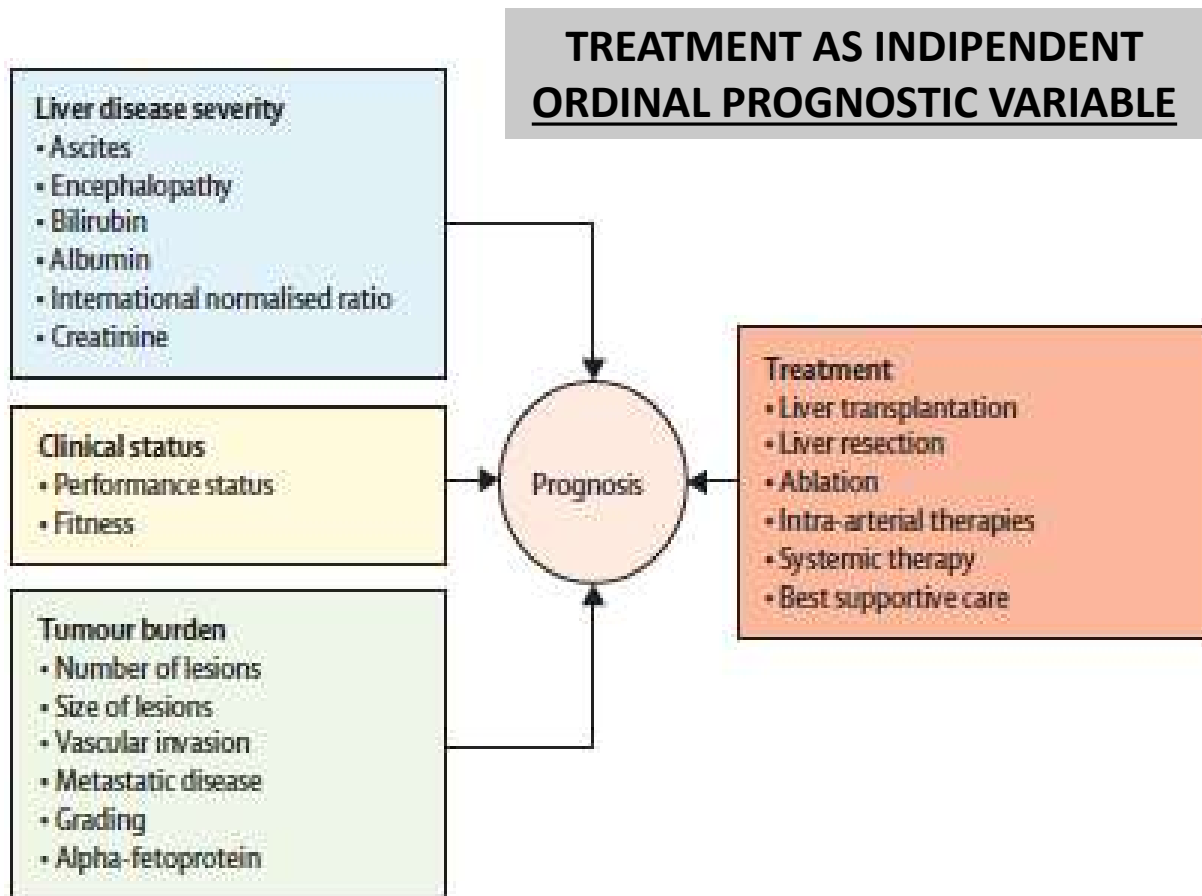
- The Ptolemaic System

Boundaries of Stage Hierarchy

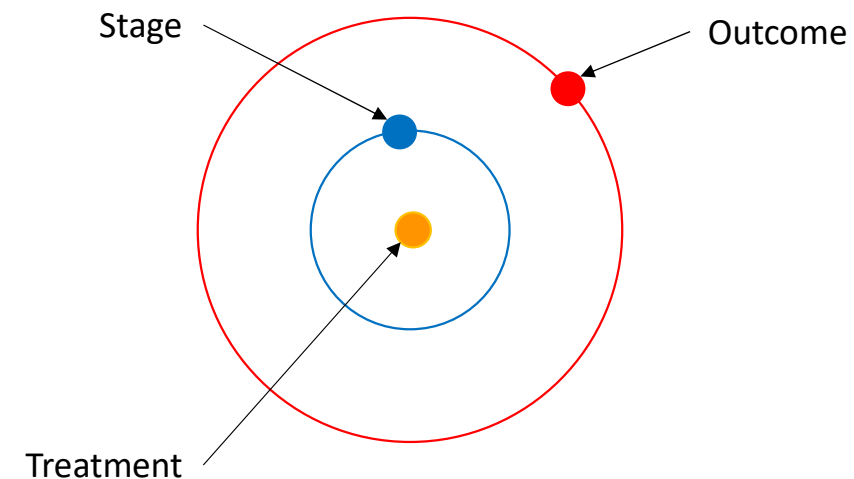
- The Copernican and Newton's evolutions



The Copernican Evolution



THERAPEUTIC HIERARCHY












Copernican Revolution

The Copernican Evolution

OVER-TREATMENT

This concept forces clinicians to adopt Personalized therapy: choice of the BEST THERAPY

**ORDINAL
THERAPEUTIC
HIERARCHY:**
independence of
the «ordinal
variable»
treatment from
staging

TUMOR STAGE											
Diameter (cm)	< 2	≤ 3	≤ 5	3-5	> 5	≤5	> 5	> 5	Any	Any	Any
Number of nodules	1	2-3	1	2-3	1	> 3	2-3	> 3	Any	Any	Any
Vascular invasion (VI) and/or metastases	No	No	No	No	No	No	No	No	Intrahep-VI	Extrahep-VI or metastases	Any
FUNCTIONAL SCORE	 CPS ≤ 9 and PST 0 or CPS ≤ 7 and PST 1- 2										 CPS 8-9 and PST 1 2, or CPS > 9, or PST > 2
STAGES	0	A	B1	B2	B3	C	D				

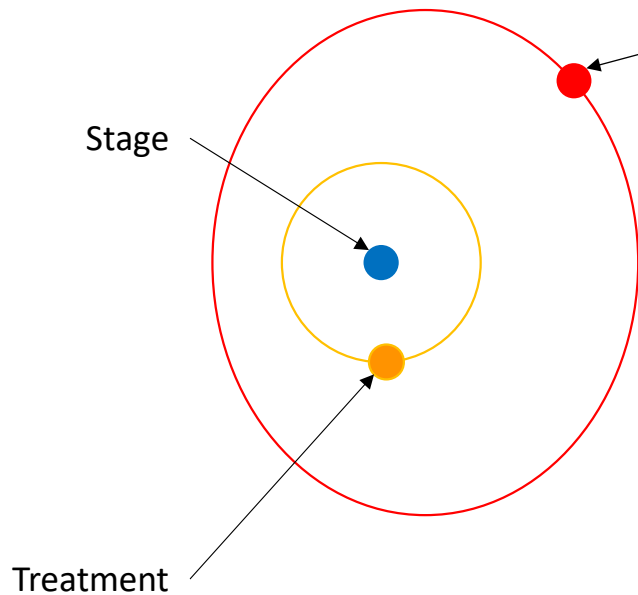
THERAPY	Expected median survival (months)						
Best supportive care	31	22	18	17	10	9	3
Systemic therapy	36	30	24	22	16	14	
Intra-arterial-therapies	55	45	35	33	23		
Ablation	80	65	50	48	33		
Liver resection	101	83	64	62	36		
Liver Transplantation	120	112	91	90			117

Expected median survival (months)



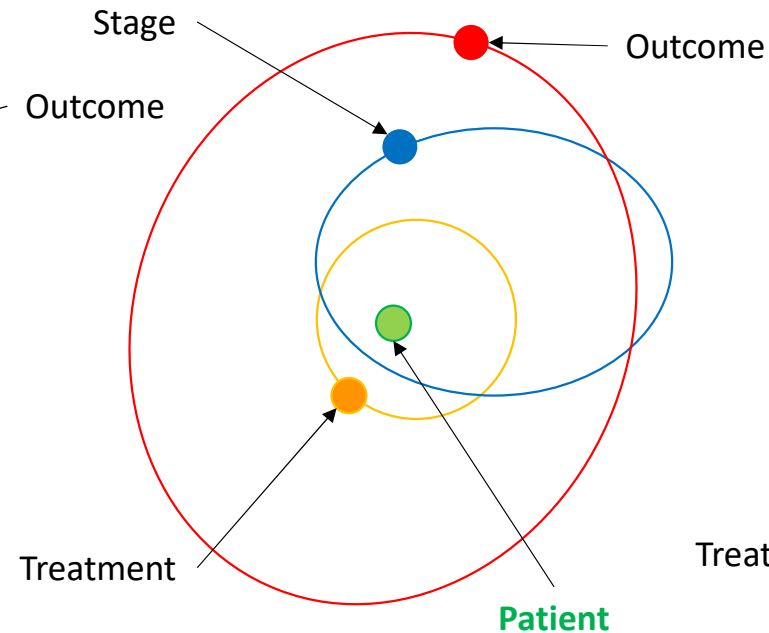
The Newton's evolution

STAGE HIERARCHY



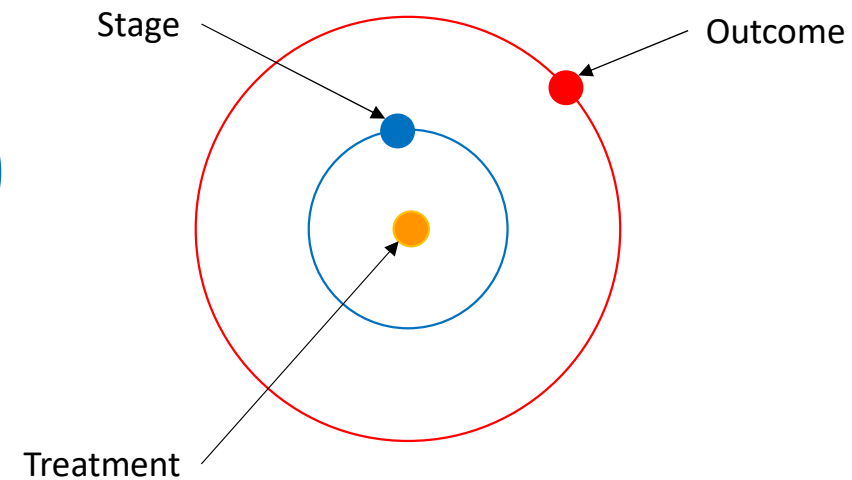
Ptolemaic System

MULTIPARAMETRIC THERAPEUTIC HIERARCHY



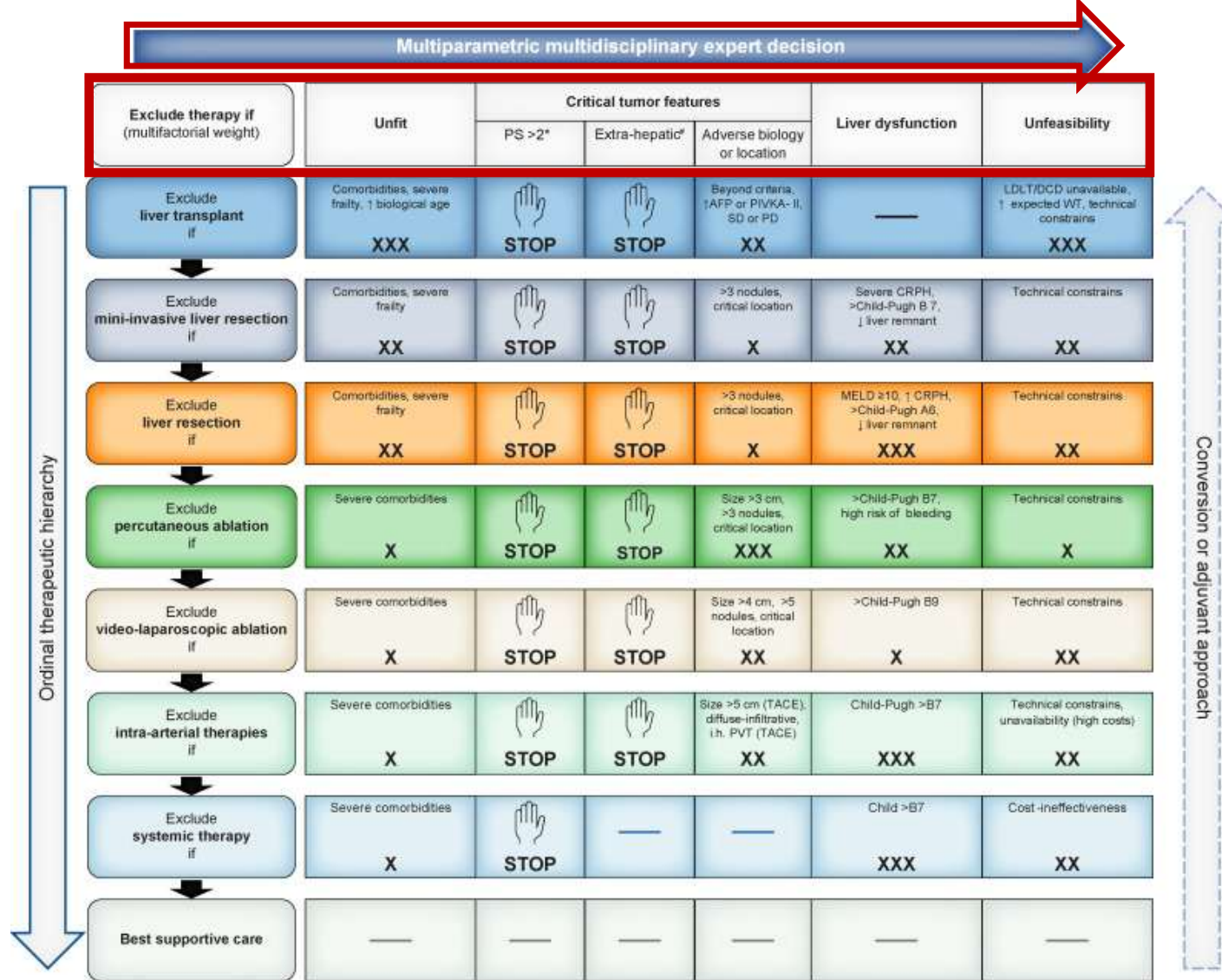
Newton's evolution

THERAPEUTIC HIERARCHY



Copernican Revolution

Multiparametric Therapeutic Hierarchy



Trevisani F, Vitale A ... J Hepatol 2024

Vitale A, et al. Lancet Oncology 2023

Multiparametric Therapeutic Hierarchy

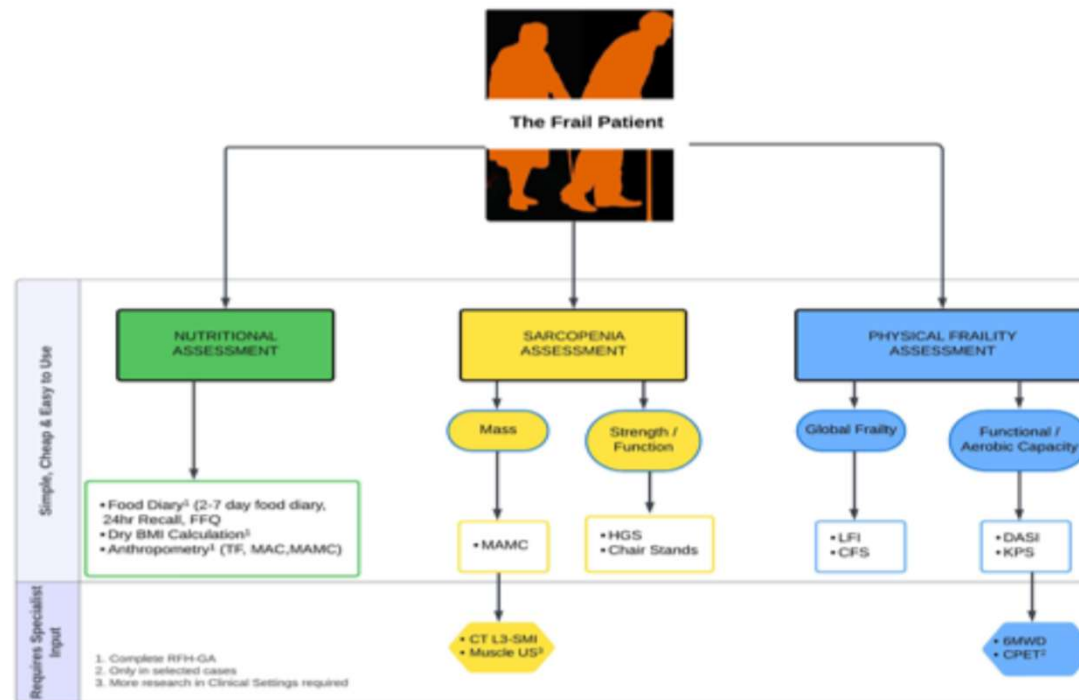
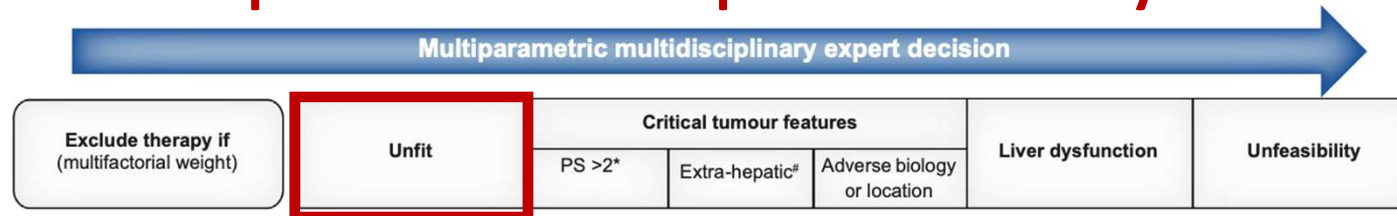
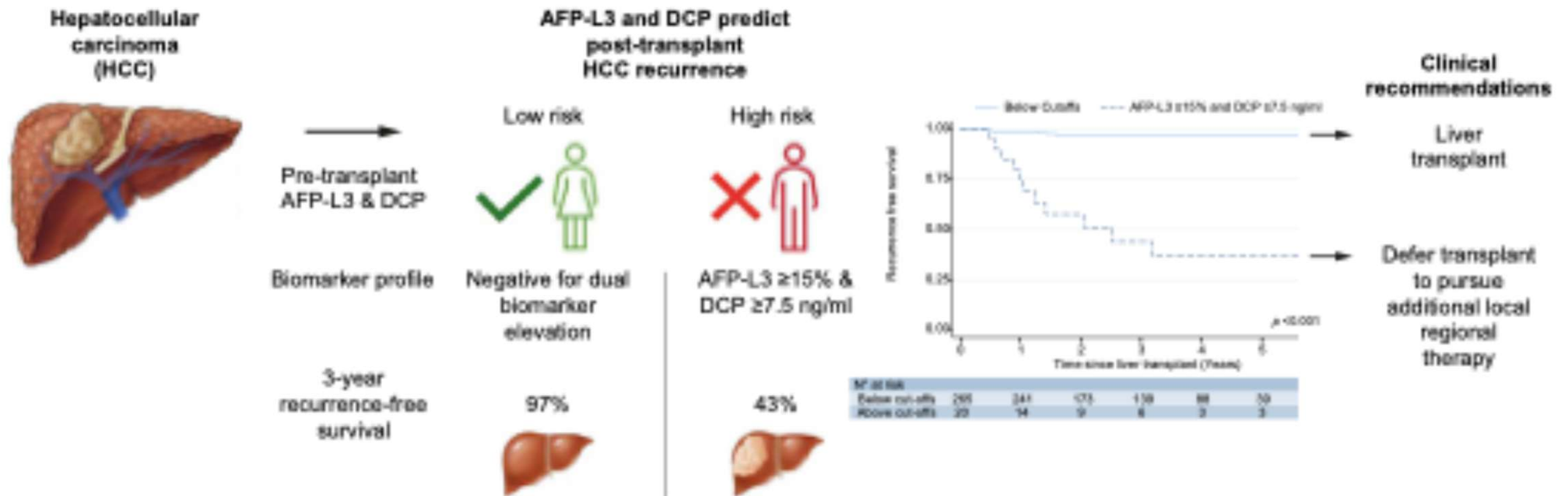
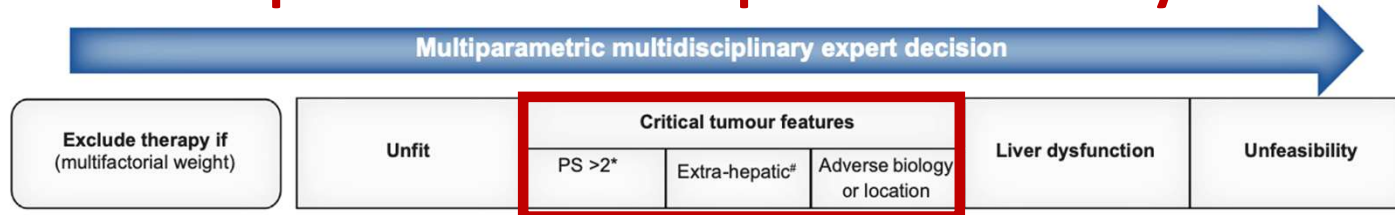


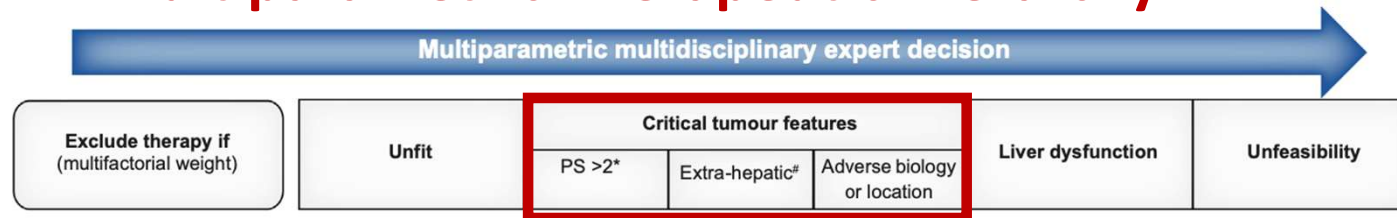
FIGURE 1. Proposed algorithm for assessing physical frailty in patients with advanced CLD. 6MWT/D, 6-min walk distance; BMI, body mass index; CFS, Clinical Frailty Scale; CLD, chronic liver disease; CPET, cardiopulmonary exercise testing; CT, computed tomography; DASI, Duke Activity Status Index; FFQ, Food Frequency Questionnaire; HGS, handgrip strength; KPS, Karnofsky performance status; L3-SMI, L3 Skeletal Muscle Index; LFI, Liver Frailty Index; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; RFH-GA, Royal Free Hospital Global Assessment; TF, triceps fold.

Multiparametric Therapeutic Hierarchy



Norman JS, et al. Journal of Hepatol 2023; 79: 1469-1477

Multiparametric Therapeutic Hierarchy



Tumor Proliferation and Pathology Markers

- MIB-1
- E-cadherin
- Nuclear beta-catenin
- Ki67
- Epithelial cell adhesion molecule
- Endothelial-cell-specific molecule-1

Angiogenesis and Inflammation Markers

- COX-2
- VEGF
- VEGF-2
- Plasma VEGF
- B-lymphocyte chemoattractant
- Interleukin-12p40

DNA-index

Circulating tumor cell

Prognostic Cell Markers and Surface Proteins

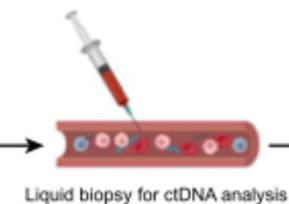
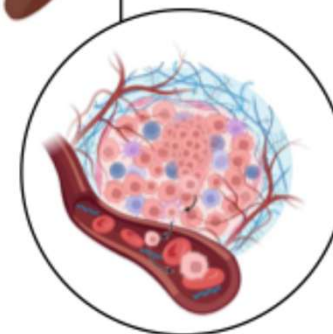
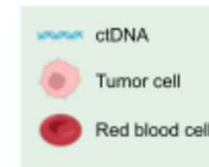
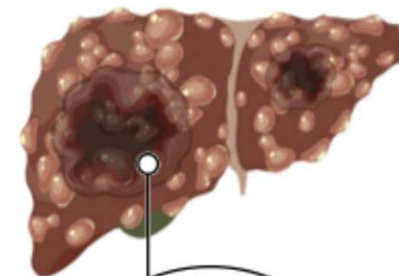
- YAP (Yes-associated protein)
- Cytokeratin-19 (CK19)
- S2
- Glypican-3 (GPC3)
- TIE2-expressing monocytes
- CD68+ tumor-associated macrophages

MicroRNAs

- miR-214
- miR-3187
- miR-148a
- miR-1246

Metabolic Profiling

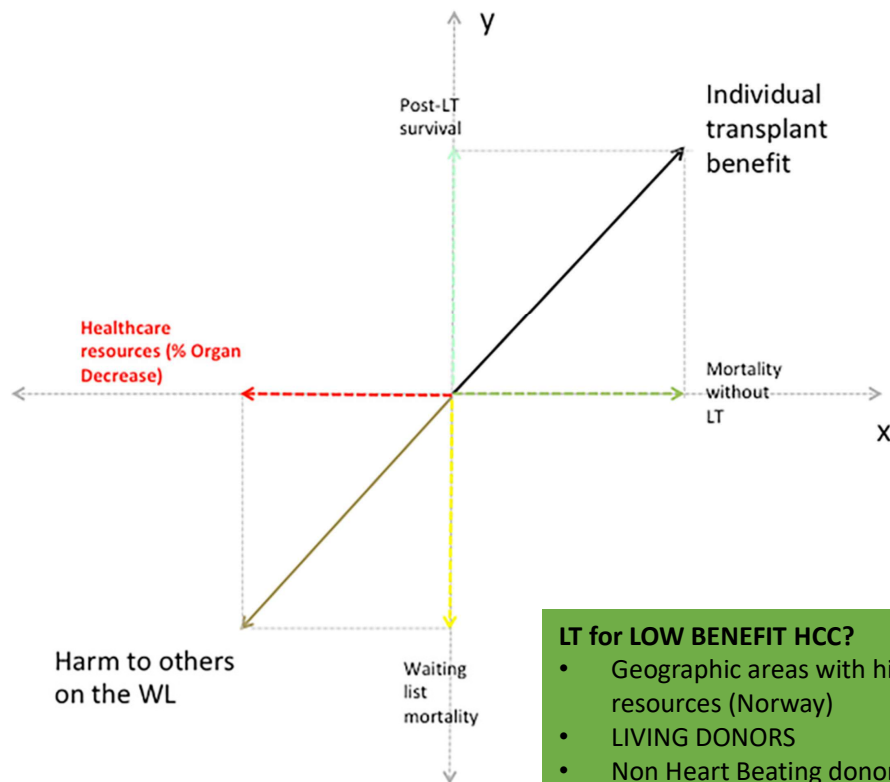
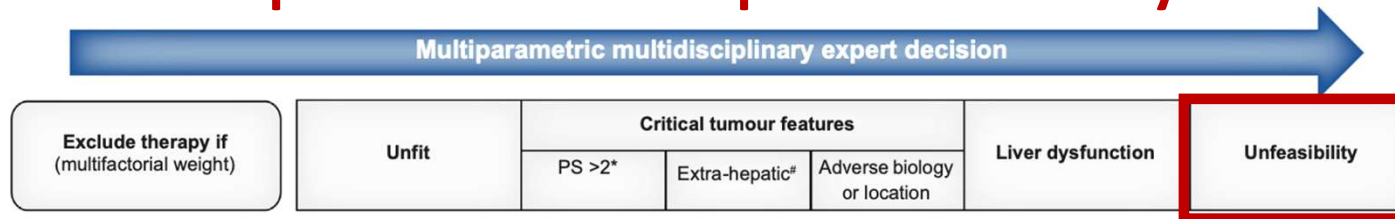
- Phosphatidylcholine 16:0/VP-18:1
- Phosphatidylcholine 18:2/OH-16:0



Possible applications

- Early detection of HCC
- Monitoring disease progression
- Determining degree of liver damage
- Prognostic use of mutation and methylation signatures
- Detection of microvascular invasion

Multiparametric Therapeutic Hierarchy



LT for LOW BENEFIT HCC?

- Geographic areas with high resources (Norway)
- LIVING DONORS
- Non Heart Beating donors
- Machine perfusion
- AB or B blood groups

Liver Transplantation for T2 Hepatocellular Carcinoma during the COVID-19 Pandemic: A Novel Model Balancing Individual Benefit against Healthcare Resources

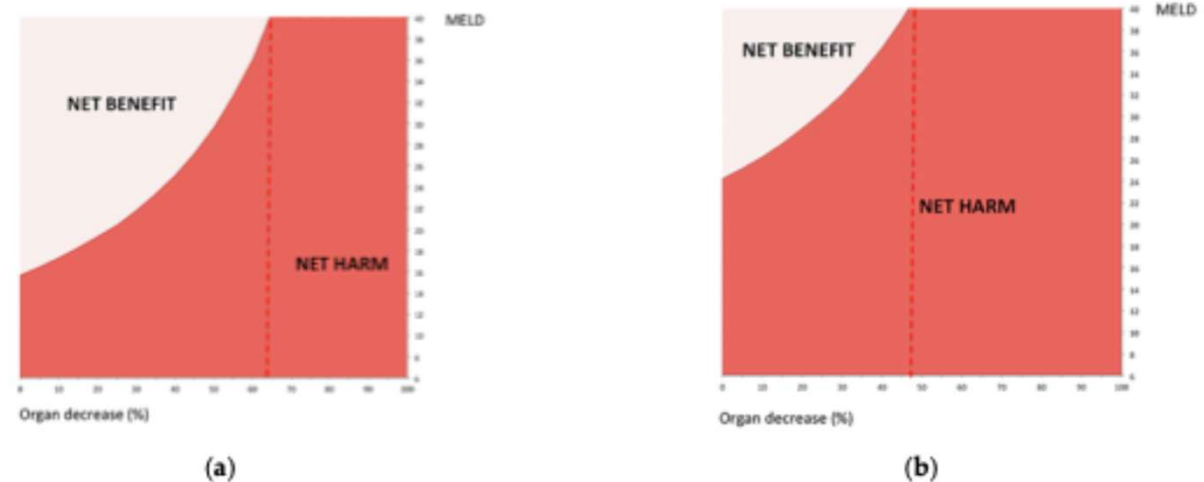


Figure 4. Impact of acute organ shortage due to COVID-19 pandemic on MELD score threshold values to decide organ allocation in T2 HCC (a) and non-HCC (b) patients.

Multiparametric Therapeutic Hierarchy

ITALIAN multi-society guidelines 2023

Recommendation: For patients with HCC, the panel recommends that the evaluation of the diagnostic and therapeutic workup be carried out by a multidisciplinary team of experts rather than by a single expert.

Certainty in evidence: Moderate.

Strength of recommendation: Strong in favor of multidisciplinary management.

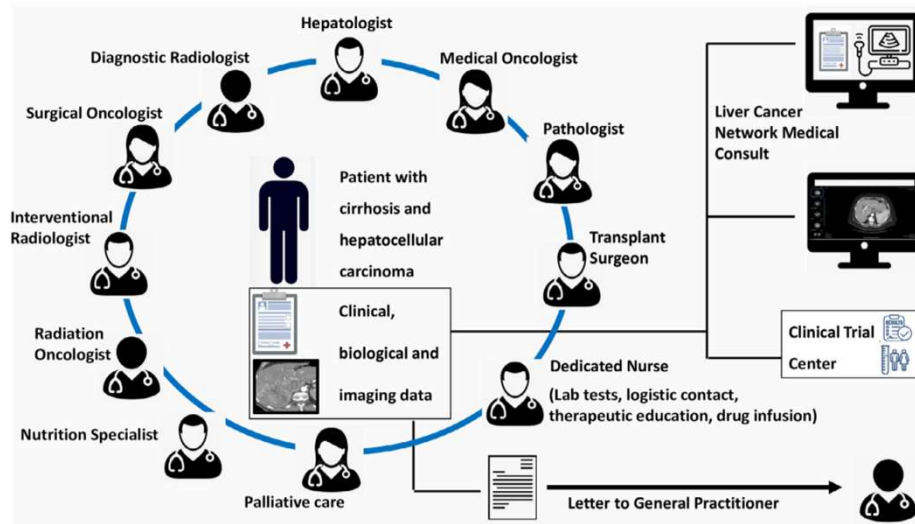
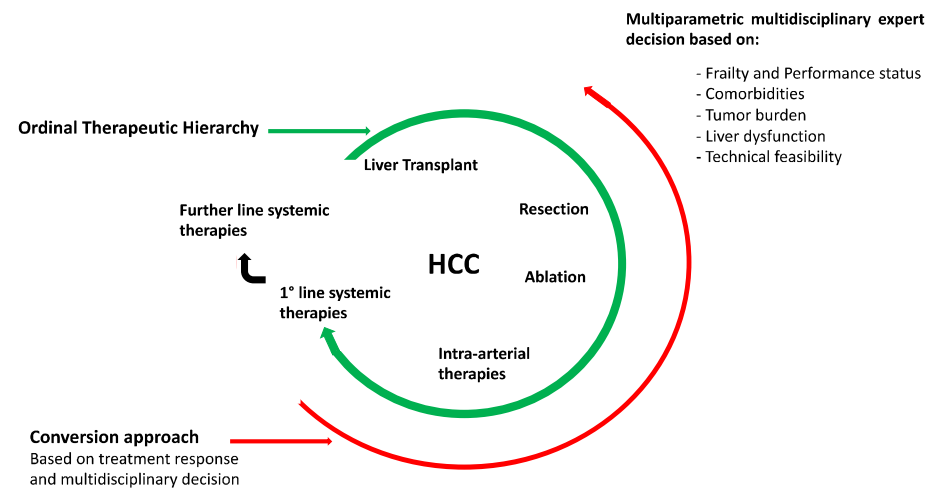


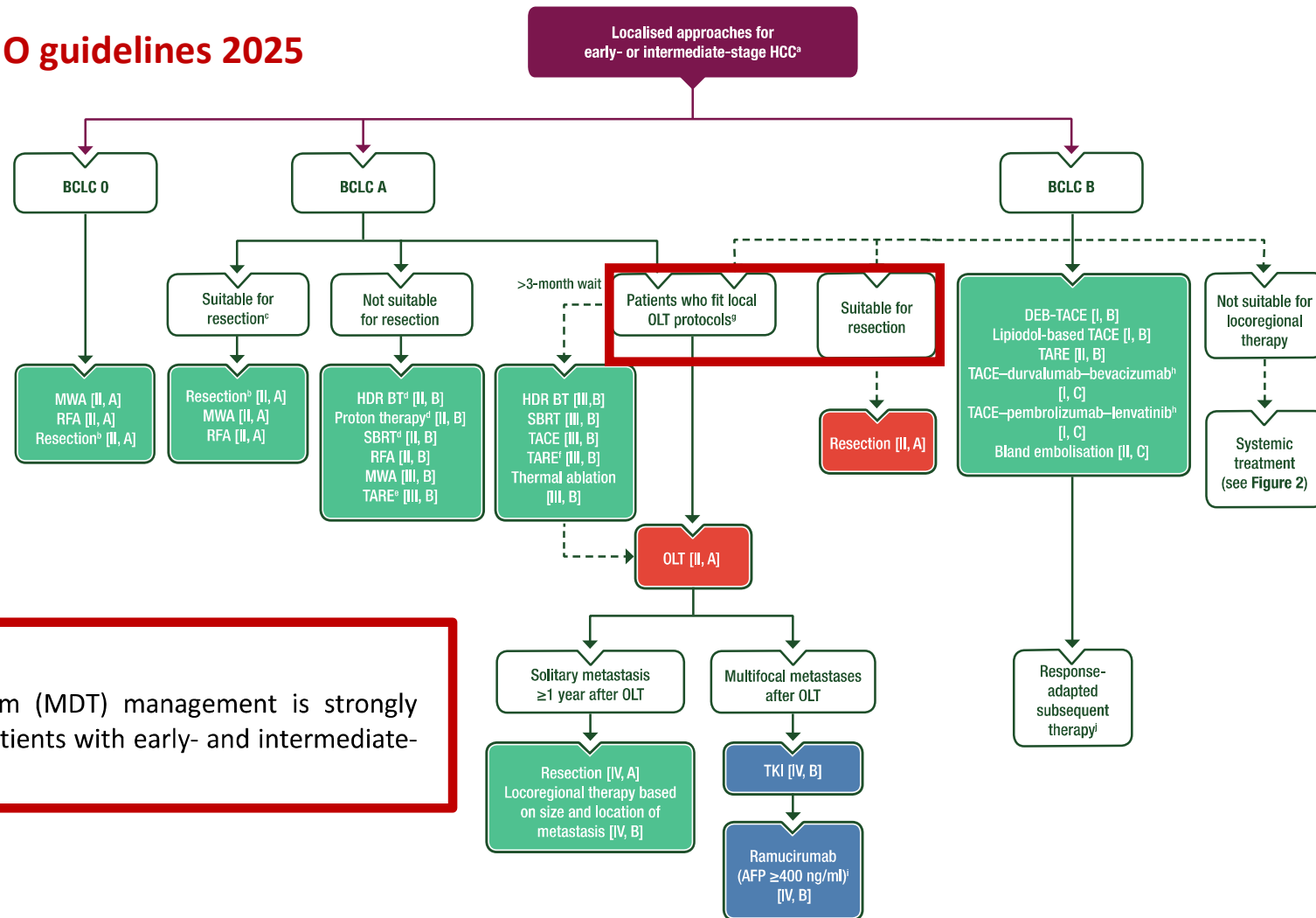
Fig. 1. Multidisciplinary tumor board.



Proposed treatment approach for patients with Hepatocellular Carcinoma, according to Therapeutic Hierarchy and multiparametric multidisciplinary expert evaluation.

Multiparametric Therapeutic Hierarchy

ESMO guidelines 2025



Multiparametric Therapeutic Hierarchy

Clinical Practice Guidelines



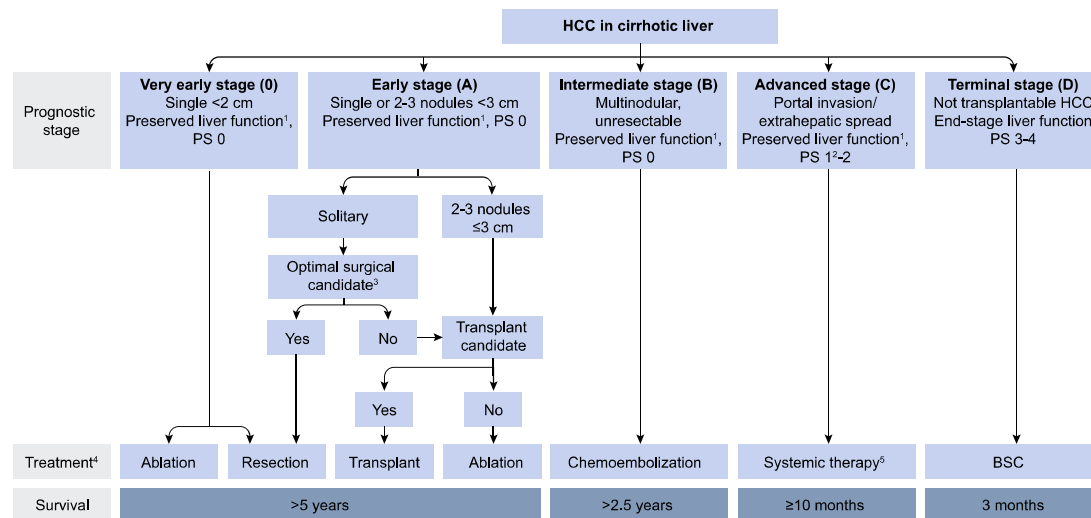
JOURNAL
OF HEPATOLOGY

Clinical Practice Guidelines

JOURNAL
OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma[☆]

European Association for the Study of the Liver^{*}



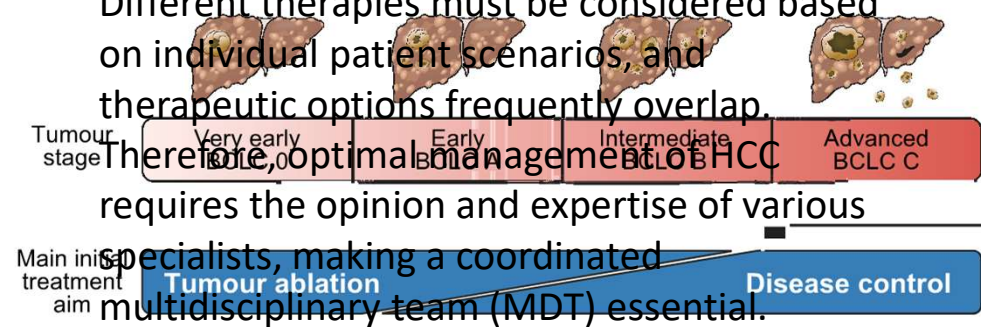
Journal of Hepatology 2018 vol. 69 | 182-236

EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma[☆]

European Association for the Study of the Liver^{*}

A multidisciplinary approach to treatment

Different therapies must be considered based on individual patient scenarios, and therapeutic options frequently overlap.



... Every patient with HCC should be assessed

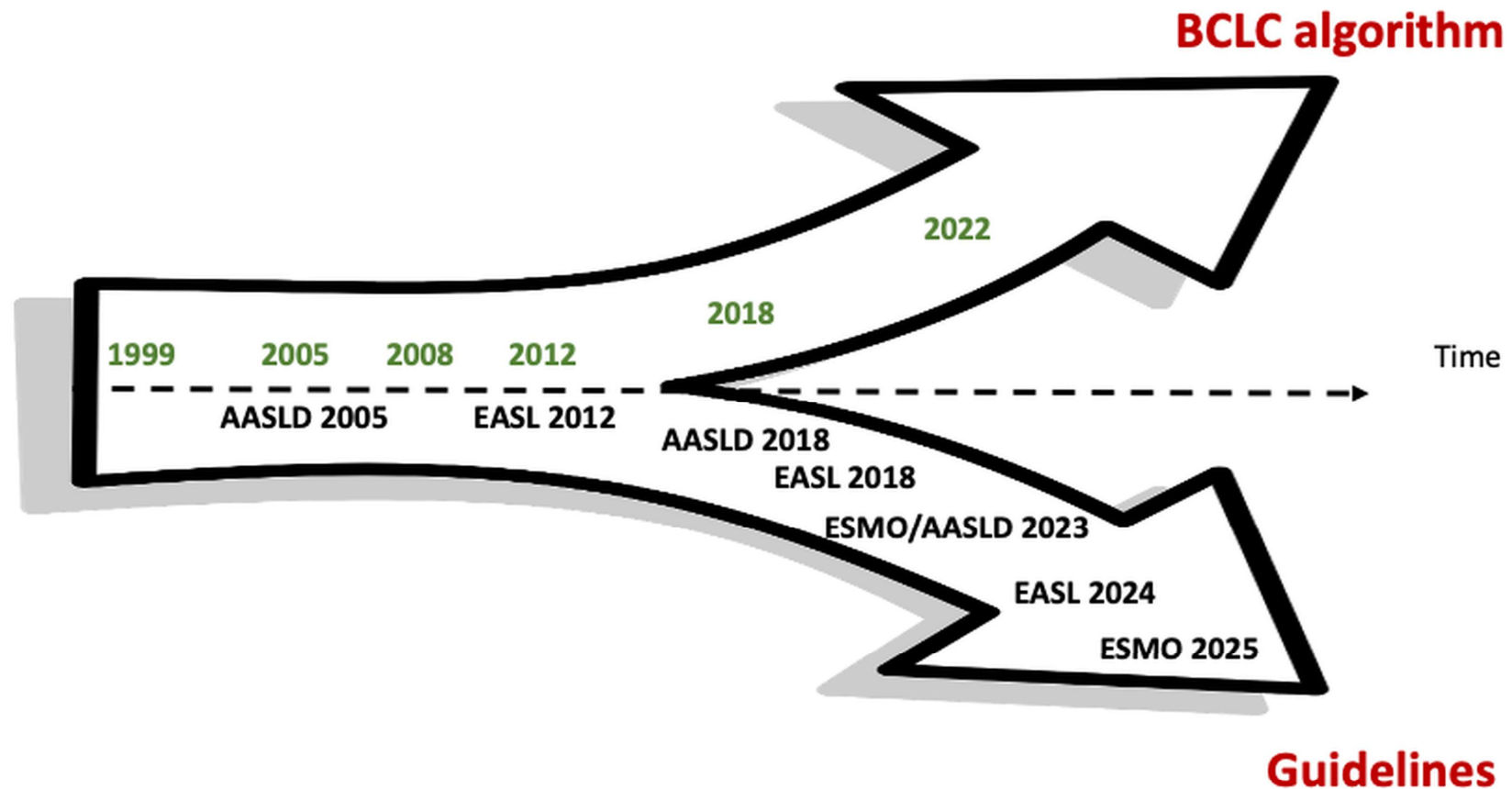
by an expert MDT at the time of initial presentation and whenever a change in treatment objectives is anticipated.

Multidisciplinary assessment and clinical decision making

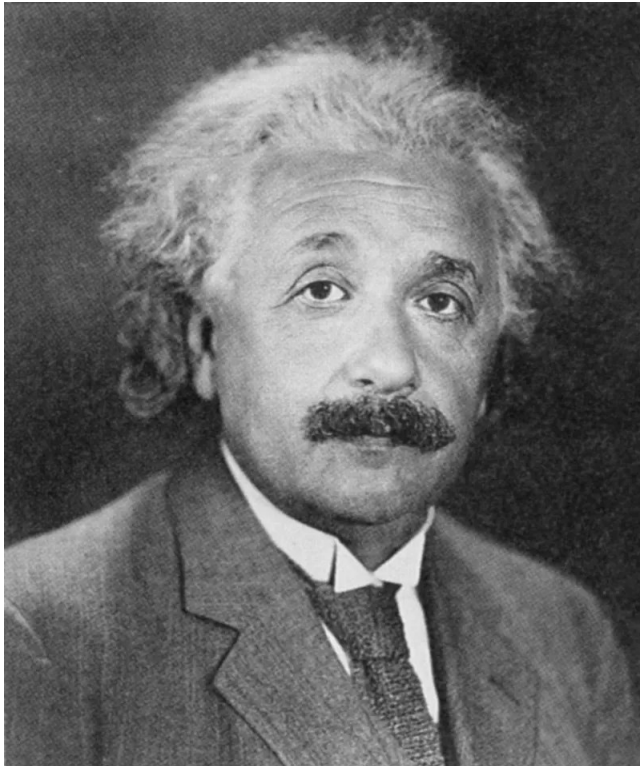
J Hepatol. 2025 Feb;82(2):315-374. doi: 10.1016/j.jhep.2024.08.028.

Multiparametric Therapeutic Hierarchy

From stage (mono-parametric) to treatment (multi-parametric) hierarchy



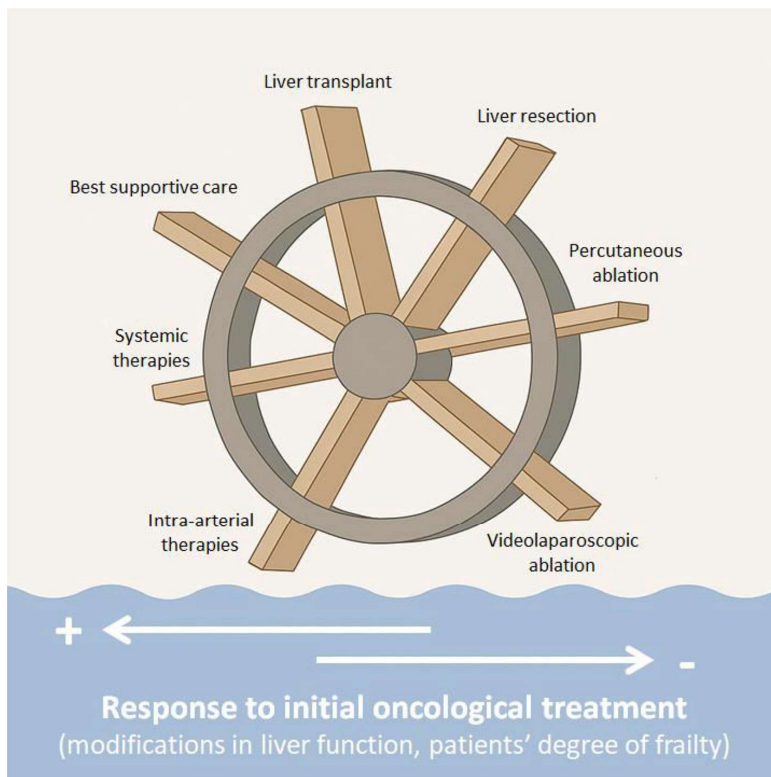
Multiparametric and Converse Therapeutic Hierarchy in HCC



- From pre-Ptolemaic to Ptolemaic era
Merits of Stage Hierarchy
- The Ptolemaic System Boundaries of Stage Hierarchy
- The Copernican and Newton's evolutions
Multiparametric Therapeutic Hierarchy and expert MDT
- The Einstein's relativity

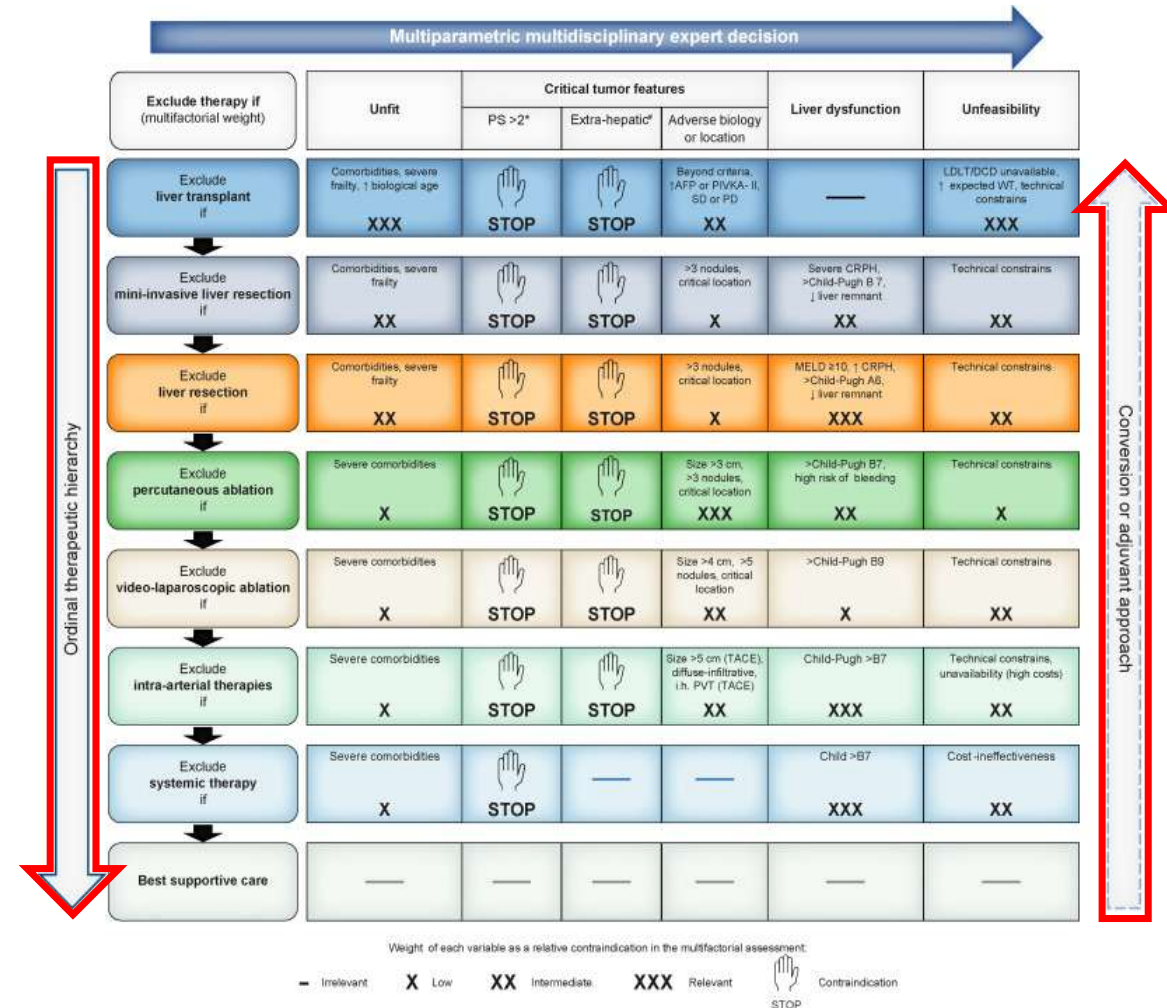
The Einstein's relativity

CONVERSION THERAPY



Giannini EG, et al. DLD 2025. In press

M Iavarone slide modified from an idea of Professor E Giannini



Trevisani F, Vitale A ... Cillo U. J Hepatol 2024

Vitale A, Cabibbo G ... Cillo U. Lancet Oncology 2023

PROBLEM 1

The Einstein's relativity CN China & JP Japan as the Master of Conversion to Resection in HCC

📌 Origin of the Concept:

Since the late 2000s, Chinese clinicians have explored combined conversion approaches (TACE, intra-arterial chemo, ablation)

📌 Concept Formalization:

In 2021, the first national Expert Consensus officially defined 'Conversion Therapy'

📌 Official Definition:

Therapy aiming to achieve radical surgical resection in patients with CNLC stage IIb, IIIa, or selected PVTT.

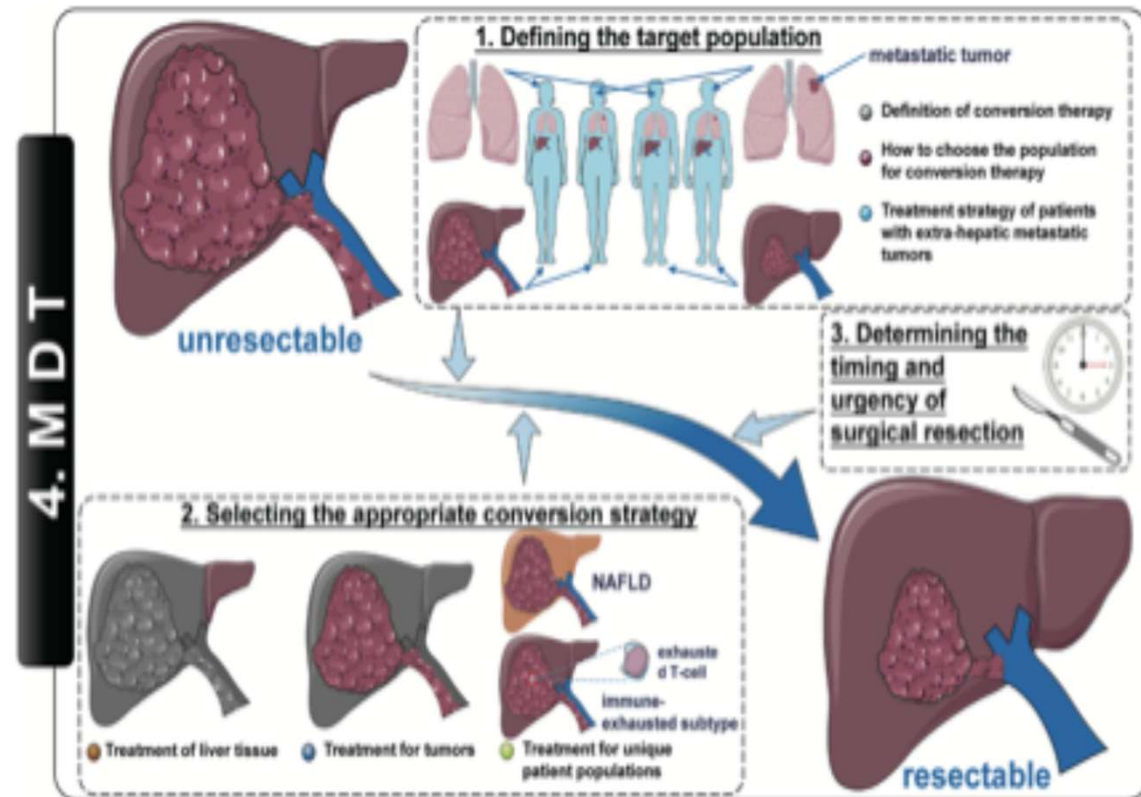
📌 Preferred Strategies:

TACETKIs / ICI, radiotherapy on PVTT, high-intensity multimodal approaches.

📌 Outcome:

Widespread clinical adoption, numerous publications, and a conceptual framework anticipating Western therapeutic hierarchies.

Sun HC et al., HepatoBiliary Surg Nutr 2022;11(2):227-252

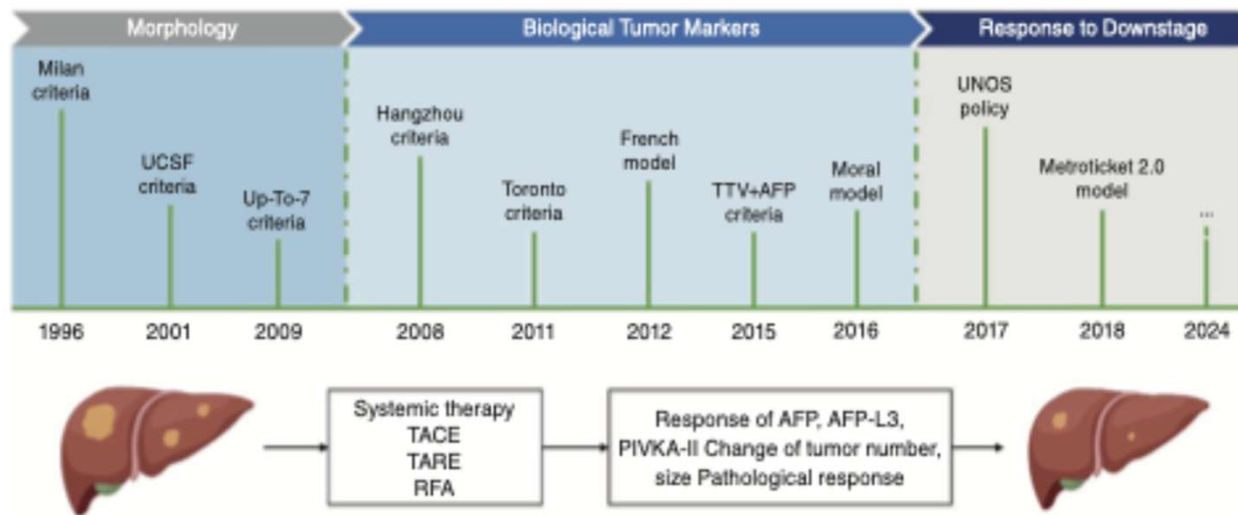


Chen QF et al., Journal of Clinical and Translational Hepatology 2024 vol. 12(3) | 298–304

PROBLEM 1

The Einstein's relativity EU Europe & us USA as Masters of Downstaging in HCC LT

- ✚ While China pioneered the concept of 'Conversion Therapy' to resection,
- ✚ Europe and the USA have led the way in 'Downstaging' strategies before liver transplantation for HCC.
- ✚ Key milestones: Milan, UCSF, Up-to-7, Hangzhou, Toronto, French model, UNOS policy, Metroticket 2.0.
- ✚ Emphasis on morphology, biological markers, and response to therapy as criteria for transplant eligibility.
- ✚ Downstaging reflects dynamic assessment: from tumor burden → biological markers → treatment response.



Sha Met al., Clinical and Molecular Hepatology 2025;31(Suppl):S285-S300

PROBLEM 2

The Einstein's relativity

Conversion to Resection in HCC

Table 5. Studies of conversion systemic therapy for HCC patients

Authors	Treatment	n	Results
Zhu et al. [58]	TKI: lenvatinib/apatinib PD-1 inhibitors: pembrolizumab/sintilizumab/camrelizumab/ nivolumab	63	Conversion rate: 19.0%
Zhang et al. [59]	TKI: lenvatinib PD-1 inhibitors: pembrolizumab/sintilizumab/toripalimab/ tiselinizumab	56	Conversion rate: 55.4% ORR: 53.6% (mRECIST), 44.6% (RECIST 1.1)
Ichida et al. [60]	Lenvatinib	49	Conversion rate: 68% ORR: 12.5% (RECIST 1.1), 37.5% (mRECIST)
Wang et al. [61]	Lenvatinib + sintilimab	36	Resection rate: 67.3% ORR: 36.1% (RECIST 1.1), 66.7% (mRECIST)
Kudo et al. [62]	Atezolizumab + bevacizumab	110	Conversion rate: 35.5% ORR: 36.4%

ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; PD-1, programmed death-1.

Recommendations

For patients with initially unachieved R0 resection or oncologically unsuitable for surgery, we recommend conversion therapy in order to undergo surgery. The successful conversion should be judged on the basis of intrahepatic disease, large vessel tumor thrombus, and extrahepatic metastasis (Recommendation I).

HIGH HETEROGENEITY IN CONVERSION RATES

Table 6. Studies of interventional therapy plus systemic therapy in the conversion therapy for HCC patients

Authors	Treatment	n	Results
Li et al. [64]	TACE + sorafenib	142	Resection rate: 14.8%
He et al. [65]	HAIC + sorafenib	125	Resection rate: 12.8% ORR: 75.2% (RECIST 1.1) 76% (mRECIST)
He et al. [66]	HAIC + sorafenib	35	Resection rate: 14.3% ORR: 40% (RECIST 1.1) 62.8% (mRECIST)
Zhang et al. [67]	HAIC+TKI+PD-1 inhibitor (TKI: sorafenib/apatinib/lenvatinib)	25	Resection rate: 56.0% pCR: 28.0% ORR: 96% (mRECIST)
He et al. [68]	Lenvatinib + toripalimab +HAIC	71	Resection rate: 12.7% ORR: 59.2% (RECIST 1.1) 67.6% (mRECIST)
Gan et al. [69]	Arterially directed therapy + lenvatinib + sintilimab	37	Conversion rate: 40.5% pCR: 8.1% ORR: 67.6% (RECIST 1.1) , 75.7%(mRECIST)
Wu et al. [70]	TACE+ lenvatinib + camrelizumab	55	Conversion rate: 54.5% pCR: 20.7% ORR: 76.4% (mRECIST)

ORR, objective response rate; pCR, pathological complete response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; TACE, Transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; PD-1, programmed death-1; TKI, tyrosine kinase inhibitor.

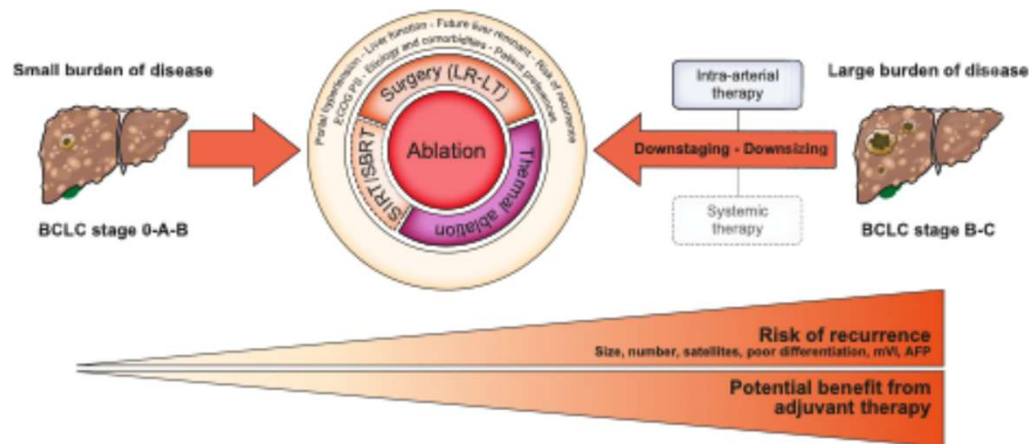
PROBLEM 3

The Einstein's relativity Conversion/Downstaging & Guidelines

The term **CONVERSION** is never mentioned!!!

Recommendations

- Patients who achieve downsizing/downstaging after locoregional treatment should be considered for liver resection or transplantation (LoE 2, strong recommendation, strong consensus).
- Patients who achieve downsizing/downstaging after systemic treatment may also be considered for liver resection or transplantation, preferably in prospective studies (LoE 3, weak recommendation, strong consensus).



EASL guidelines. J Hepatol. 2025; 82:315-374.

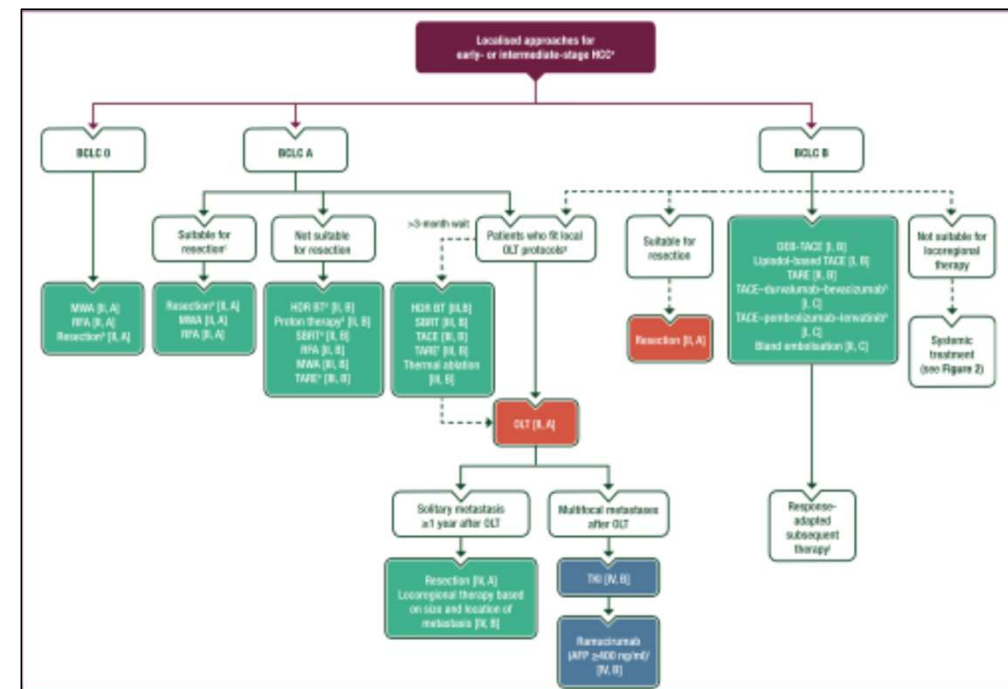
SPECIAL ARTICLE

Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]

A. Vogel^{1,2,3}, S. L. Chan⁴, L. A. Dawson^{5,6}, R. K. Kelley⁷, J. M. Llovet^{8,9,10}, T. Meyer^{11,12}, J. Ricke¹³, L. Rimassa^{14,15}, G. Sapisochin¹⁶, V. Vilgrain^{17,18}, J. Zucman-Rossi¹⁹ & M. Ducreux^{20,21}, on behalf of the ESMO Guidelines Committee^{*}

Volume 36 ■ Issue 5 ■ 2025

<https://doi.org/10.1016/j.jannonc.2025.02.006> 491



Converse Therapeutic Hierarchy

Neoadjuvant intent therapy

ONCOLOGICAL CRITERIA
(biological)

Bad (unsuitable)
Intermediate (borderline suitable)
Good (suitable)

Perioperative camrelizumab plus rivoceranib versus surgery alone in patients with resectable hepatocellular carcinoma at intermediate or high risk of recurrence (CARES-009): a randomised phase 2/3 trial

Zheng Wang, Jia Fan*, Shaolai Zhou, Yunfan Sun, Fei Liang, Yuan Ji, Fangming Gu, Tao Li, Li Peng, Tao Peng, Xiaolun Huang, Zhenbin Ding, Dousheng Bai, Bangde Xiang, Guang Tan, Tianfu Wen, Yongyi Zeng, Feng Han, Yu Zhang, Shengdong Wu, Haitao Zhao, Yi Chen, Guoming Shi, Zhiguo Hou, Ying Sun, Wenqing Zhu, Jian Zhou*

www.thelancet.com Published online October 19, 2025 [https://doi.org/10.1016/S0140-6736\(25\)01720-9](https://doi.org/10.1016/S0140-6736(25)01720-9)

Patient suitable for neoadjuvant intent therapy
(LRT ± systemic therapy/
non-oncological procedures)

Patient suitable for upfront curative intent therapy

Easy
(suitable)

Intermediate
(borderline suitable)

Difficult
(unsuitable)

CARES-009 stud
CARES-009 is a multi-center, pha

Key eligibility criteria:

- CNLC Ib/Ia/Ib/Ia (excluding Vp4) HCC^a
- No prior systemic therapy
- Child-Pugh class A
- ECOG PS 0-1
- Adequate organ function

N=294

Stratification factors:

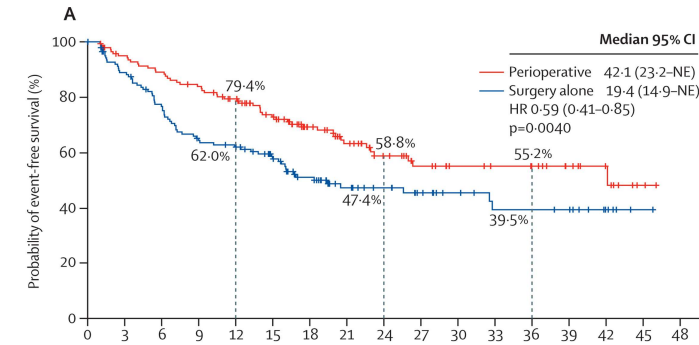
- CNLC stage (Ib vs. IIa-IIb vs. IIIa)
- HBV infection status (positive vs. negative)

• At data cutoff (March 30 2025), t

CNLC, China Liver Cancer Staging.
a. CNLC Ib/Ia/Ib/Ia corresponds to Barcelona Clinic Liver Cancer (BCLC) without Vp4 involvement or extrahepatic recurrence

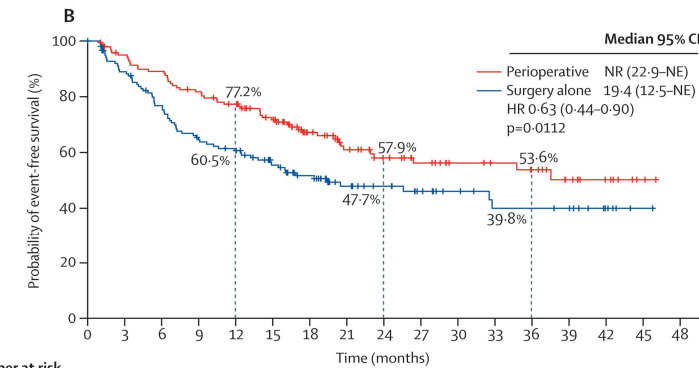
Jian Zhou

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Number at risk (censored)

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Perioperative	148	129	121	113	103	87	63	50	37	29	24	22	18	13	8	2	0
Surgery alone	146	118	100	83	78	65	48	33	28	22	17	13	13	12	5	1	0



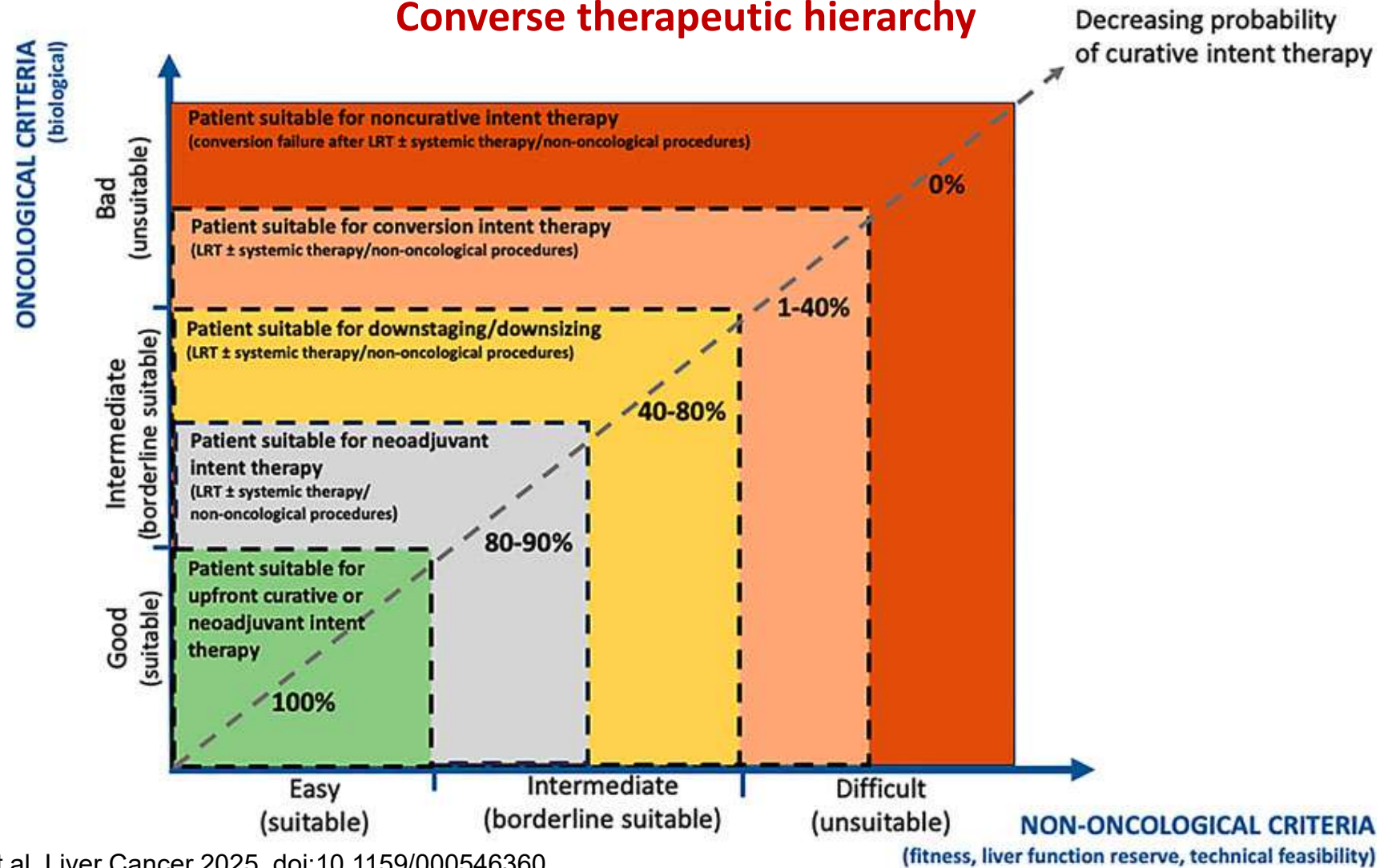
Number at risk (censored)

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Perioperative	148	129	121	110	102	87	60	47	37	31	25	23	18	12	7	2	0
Surgery alone	146	118	100	83	76	61	48	33	28	22	17	13	13	12	5	1	0

NON-ONCOLOGICAL CRITERIA
(fitness, liver function reserve, technical feasibility)

The Einstein's relativity

Converse therapeutic hierarchy



Converse Therapeutic Hierarchy

TALENTOP: Phase 3 study of surgical resection followed by maintenance Atezolizumab + Bevacizumab (Atezo + Bev) versus sustained Atezo + Bev in hepatocellular carcinoma patients with macrovascular invasion after initial Atezo + Bev conversion treatment.

Conclusions

- For HCC patients with macrovascular invasion who achieved PR or SD and eligible for resection after initial Atezo + Bev treatment, liver resection followed by maintenance Atezo + Bev treatment provided statistically significant and clinically meaningful benefits compared to sustained Atezo + Bev treatment.
 - This study met its primary endpoint of TTF (HR, 0.60; $P=0.015$).
 - OS data remain immature, while a trend toward benefit is observed (HR, 0.67; 95% CI, 0.35-1.29).
 - The safety of surgical resection after initial Atezo + Bev treatment is manageable.
- These results of the TALENTOP study underscore the efficacy of the Atezo + Bev regimen as conversion treatment in advanced HCC patients.
- Patients with advanced HCC who have responded to systemic therapy may be candidates for surgical resection.

Presented by Hui-Chuan Sun

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Multiparametric and Converse Therapeutic Hierarchy in HCC



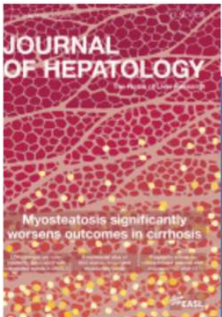
- From pre-Ptolemaic to Ptolemaic era
Merits of Stage Hierarchy
- The Ptolemaic System
Boundaries of Stage Hierarchy
- The Copernican and Newton's evolutions
Multiparametric Therapeutic Hierarchy and expert MDT
- The Einstein's relativity
Converse Therapeutic Hierarchy
- The Heisenberg's uncertainty

The Heisenberg's uncertainty

Letter to the Editor

JOURNAL
OF HEPATOLOGY

Hazardous journeys



Evidence and choice: The BCLC vision for tailoring clinical decision-making

Maria Reig^{1,2,3,4,*} Ángeles García-Criado^{1,4,5}
Alejandro Forner^{1,2,3,4} Robin K. Kelley⁸
Jordi Rimola^{1,5} Peter R. Galle⁹
Joana Ferrer-Fàbrega^{1,3,4,6} Vincenzo Mazzaferro¹⁰
Marta Burrel^{1,4,7} Riad Salem¹¹
Bruno Sangro^{3,12}
Amit G. Singal¹³
Arndt Vogel^{14,15}
Josep Fuster^{1,3,4,6}
Carmen Ayuso^{1,3,4,5}
Jordi Bruix¹

Journal of Hepatology, **October 2024**. vol. 81 | e176–e177

Their 'hierarchical approach'¹ lacks the same scientific rigor, presenting a contradiction by demanding methodological rigor in prognosis but not in treatment. This inconsistency underlines a flaw in their argument, **with most supporting cohorts biased, undermining robust conclusions. Only prospective trials can offer reliable recommendations**, underscoring the undervalued potential of systemic therapies in various HCC stages and suggesting a need to revise current treatment approaches

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

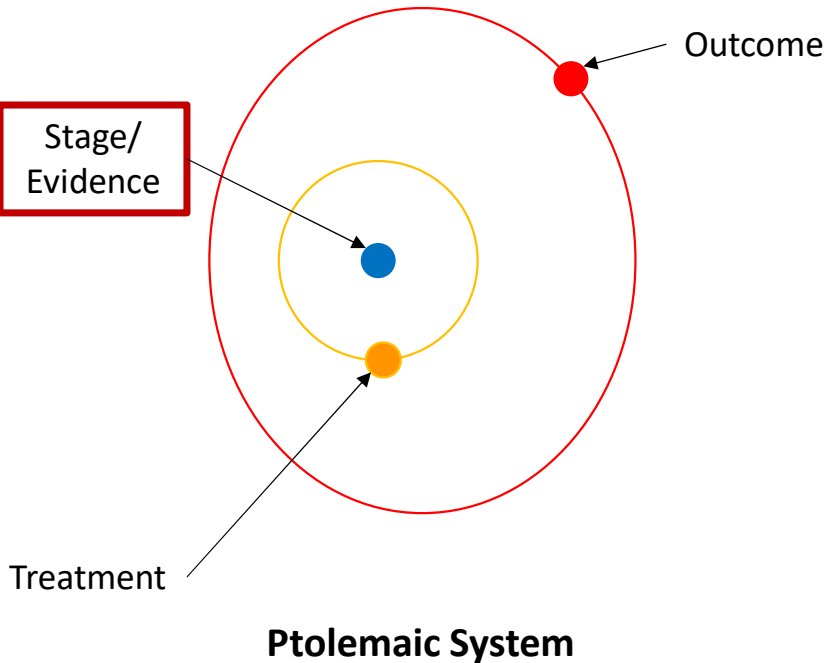


Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

BMJ 2003;327:1459–61

The Heisenberg's uncertainty

STAGE/EVIDENCE HIERARCHY



BCLC stage	Treatment (standard of care)	Indication constraints based on tumour burden and liver function	Alternative treatment
0-A Single tumour any size or up to three nodules ≤ 3 cm Preserved liver function ECOG PS 0	Resection [III, A] Transplantation [III, A] Thermal ablation [III, A] TACE [I, A]	Adequate size and function of remnant liver Size ≤ 5 cm, number of nodules ≤ 3 Size ≤ 3 cm, not adjacent to vessels or bile duct Contraindications against resection and thermal ablation. Bridging to transplantation	SBRT [III, C] HDR brachytherapy [III, C] SIRT [III, C]
B Multinodular Preserved liver function ECOG PS 0	TACE [I, A]	Size 5-10 cm, tumour nodules accessible to supra-selective catheterisation	Transplantation [III, A] Resection [III, A] Systemic therapy (not suitable for local therapies) [I, A] SIRT (liver confined, good liver function, no systemic therapy feasible) SIRT (liver confined, good liver function, no systemic therapy feasible)
C Portal invasion Extrahepatic spread Preserved liver function ECOG PS 0-2	Atezolizumab plus bevacizumab (first line) [I, A; ESMO-MCBS v1.1 score: 5] Option: Sorafenib (first line) [I, A; ESMO-MCBS v1.1 score: 4] Lenvatinib (first line) [I, A] ^a Standard after sorafenib: Cabozantinib [I, A; ESMO-MCBS v1.1 score: 3] Regorafenib ^b [I, A; ESMO-MCBS v1.1 score: 4] Ramucirumab ^c [I, A; ESMO-MCBS v1.1 score: 1] Option after atezolizumab plus bevacizumab/lenvatinib: Sorafenib [V, C] Lenvatinib [V, C] Cabozantinib [V, C] Regorafenib ^b [V, C] Ramucirumab ^c [V, C]	Child–Pugh A Child–Pugh A Tolerability to sorafenib, (regorafenib) AFP ≥ 400 ng/ml for ramucirumab	
D End-stage liver function ECOG PS 3-4	BSC [III, A]		

The Heisenberg's uncertainty

Letter to the Editor

JOURNAL
OF HEPATOLOGY

Reply to: “Evidence and choice: The BCLC vision for tailoring clinical decision-making”

Evidence-based failure of stage hierarchy therapeutic approach to HCC

Franco Trevisani^{1,2,†}

Alessandro Vitale^{3,*†}

Agostino Colli⁴

Masatoshi Kudo⁵

Laura Kulik⁶

Joon-Won Park⁷

David J. Pinato^{8,9}

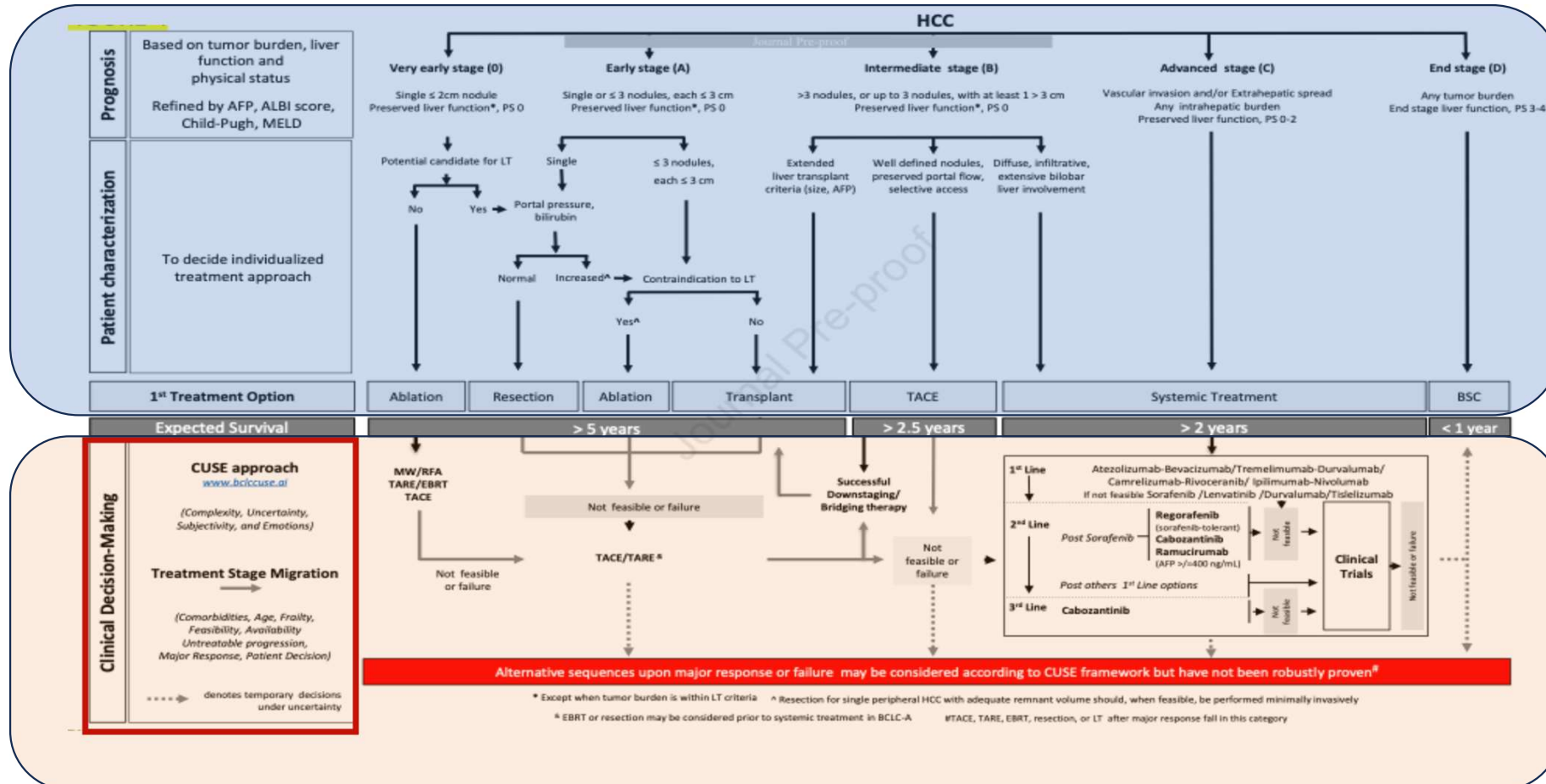
Umberto Cillo³

Journal of Hepatology, October 2024. vol. 81 | e178–e180

Furthermore, according to GRADE, the strength of a recommendation depends not only on the certainty of evidence but also on the consideration of the **balance between treatment benefits and harms, societal values and preferences, resources, feasibility, acceptability, and equity**.³ Thus, the absence of prospective trials comparing treatments does not necessarily preclude making evidence-based assumptions, ultimately leading to strong recommendations. **From this perspective, the BCLC 2022 lacks a systematic analysis and grading of all available evidence, whereas MTH is much more inclusive.**

The Heisenberg's uncertainty

HIGH CERTAINTY OF EVIDENCE → 1° Treatment Option



UNCERTAINTY OF EVIDENCE → Alternative personalised options

Reig M, et al. J Hepatol. 2025; Oct 27:S0168-8278(25)02571-1. doi: 10.1016/j.jhep.2025.10.020.

CERTAINTY OF SURVIVAL BENEFIT EVIDENCE

EXCLUDE THERAPY IF
(multifactorial weight)

Exclude
liver transplant
if

Exclude
Mini-invasive liver Resection
if

Exclude
liver resection
if

Exclude
percutaneous ablation
if

Exclude
video-laparoscopic ablation
if














Exclude
intra-arterial therapies
if

Exclude
systemic therapy
if

Best supportive care

INDIVIDUAL RECOMMENDATION

MULTIPARAMETRIC MULTIDISCIPLINARY EXPERT DECISION

BENEFITS (desirable effects)			HARMS (undesirable effects)	HARMS/BURDEN/VALUES AND PREFERENCES	FEASIBILITY, RESOURCES, ACCEPTABILITY, EQUITY
CRITICAL TUMOR FEATURES			LIVER DYSFUNCTION	UNFIT	UNFEASIBILITY
PS > 2	Extra-hepatic*	Adverse biology or location			
 STOP	 STOP	Beyond criteria, ↑ AFP or PIVKA-II, SD or PD XX	—	Comorbidities, severe frailty, ↑ biological age XXX	LDLT / DCD unavailable, ↑ expected WT, technical constraints XXX
 STOP	 STOP	> 3 nodules, critical location X	Severe CRPH, > Child B 7, ↓ liver remnant XX	Comorbidities, severe frailty XX	Technical constraints, XX
 STOP	 STOP	> 3 nodules, critical location X	MELD ≥ 10, ↑ CRPH, > Child A6, ↓ liver remnant XXX	Comorbidities, severe frailty XX	Technical constraints XX
 STOP	 STOP	Size > 3 cm, > 3 nodules, critical location XXX	> Child B7, high risk of bleeding XX	Severe comorbidities X	Technical constraints X
 STOP	 STOP	Size > 4 cm, > 5 nodules, critical location XX	> Child B9 X	Severe comorbidities X	Technical constraints XX
 STOP	 STOP	Size > 5 cm (TACE), diffuse-infiltrative, i.h. PVT (TACE) XX	Child > B7 XXX	Severe comorbidities X	Technical constraints, unavailability (high costs) XX
 STOP	—	—	Child > B7 XXX	Severe comorbidities X	cost-ineffectiveness XX
—	—	—	—	—	—

The Heisenberg's uncertainty: the MTH-EtD proposal

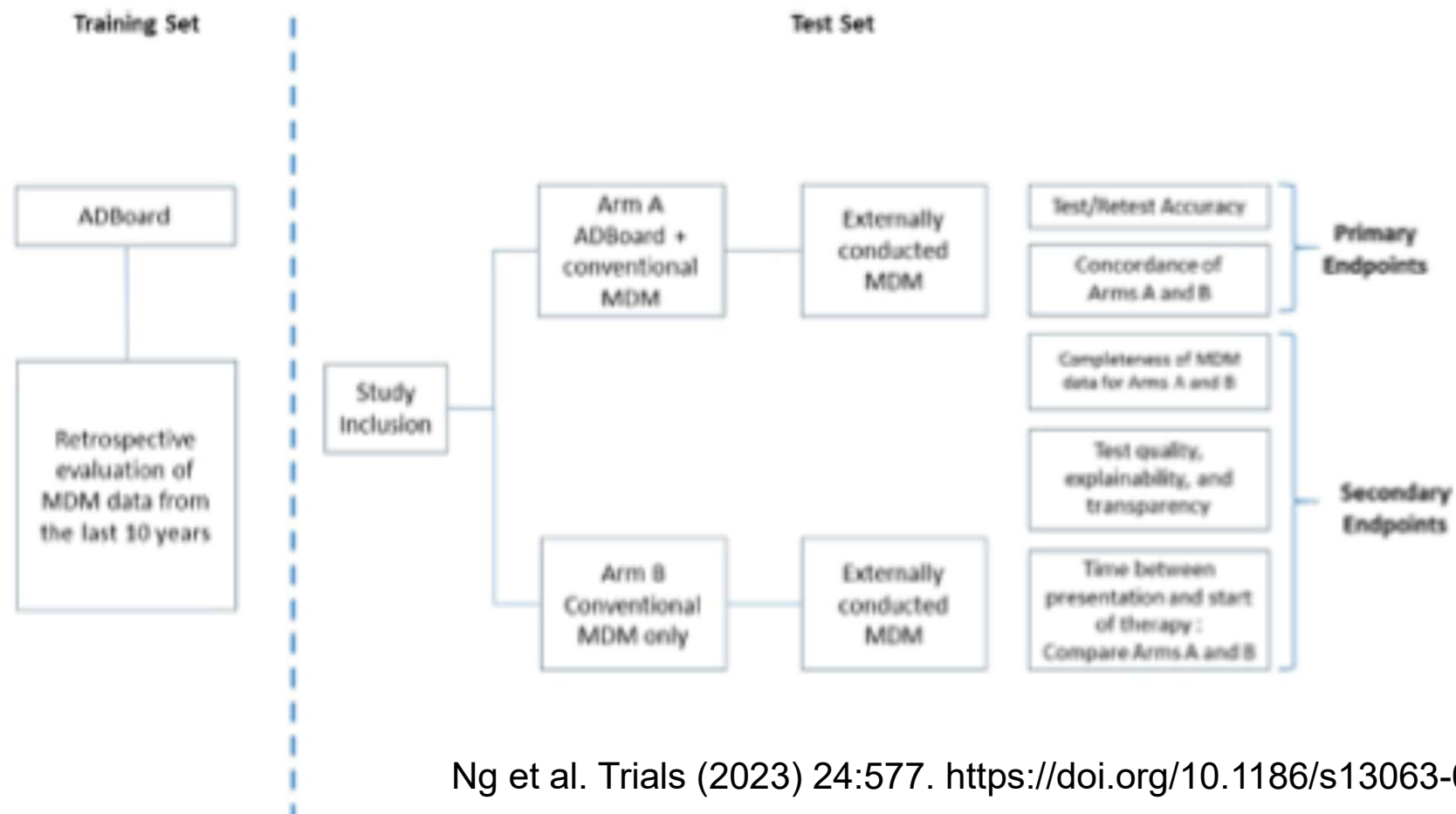
MTH, «GRADE inspired» as a complete EtD framework for individual therapeutic decision-making

- Transform MTH into a GRADE inspired Evidence-to-Decision tool for expert MDT meetings
- Map each MTH dimension to GRADE EtD domains (benefits, harms, burden/values, feasibility/resources/equity)
- Provide a transparent, reproducible, patient-centred decision pathway

CERTAINTY OF SURVIVAL BENEFIT EVIDENCE		INDIVIDUAL RECOMMENDATION MULTIPARAMETRIC MULTIDISCIPLINARY EXPERT DECISION					
ORDINAL THERAPEUTIC HIERARCHY		✓ BENEFITS (desirable effects + certainty)			✗ HARMS (undesirable effects)	⚖ HARMS/BURDEN/VALUES (harms + burden + patient values/preferences)	⦿ FEASIBILITY (feasibility, resources, acceptability, equity)
	Exclude therapy if (multifactorial weight)	CRITICAL TUMOR FEATURES			LIVER DYSFUNCTION	UNFIT	UNFEASIBILITY
		PS > 2	Extra-hepatic*	Adverse biology or location			
	Exclude liver transplant if	STOP	STOP	Beyond criteria, P-AFP or PIVKA-II, SD or PD XX	●	Comorbidities, severe frailty, ↑ biological age XXX	LDLT / DCD unavailable, ↑ expected WT, technical constrains XXX
	Exclude Mini-invasive liver Resection if	STOP	STOP	> 3 nodules, critical location X	Severe CRPH, > Child B 7, ↓ liver remnant XX	Comorbidities, severe frailty XX	Technical constrains XX
	Exclude liver resection if	STOP	STOP	> 3 nodules, critical location X	MELD > 10, ↑ CRPH, > Child A6, ↓ liver remnant XXX	Comorbidities, severe frailty XX	Technical constrains XXX
	Exclude percutaneous ablation if	STOP	STOP	Size > 3 cm, > 3 nodules, critical location XXX	> Child B7, high risk of bleeding XX	Severe comorbidities X	Technical constrains X
	Exclude video-laparoscopic ablation if	STOP	STOP	Size > 4 cm, > 5 nodules, critical location XX	> Child B9 X	Severe comorbidities X	Technical constrains XX
	Exclude intra-arterial therapies if	STOP	STOP	Size > 5 cm (TACE), diffuse- infiltrative, IH, PVT (TACE) XX	Child > B7 XXX	Severe comorbidities X	Technical constrains, unavailability (high costs) XX
	Exclude systemic therapy if	STOP	●	●	Child > B7 XXX	Severe comorbidities X	cost-ineffectiveness XX
Best supportive care	●	●	●	●	●	●	
<div> GRADE Legend</div> <div>STOP = Net harm → strong against XXX = Severe negative impact → conditional against XX = Moderate impact → conditional X = Mild impact → direction unchanged ● = Irrelevant / EtD-neutral</div>							

The Heisenberg's uncertainty: the digital MTH-EtD proposal

Therapeutic Assistance and Decision algorithms for hepatobiliary tumor Boards (ADBoard) aim to reduce this delay by providing automated data extraction and high-quality, evidence-based treatment recommendations.

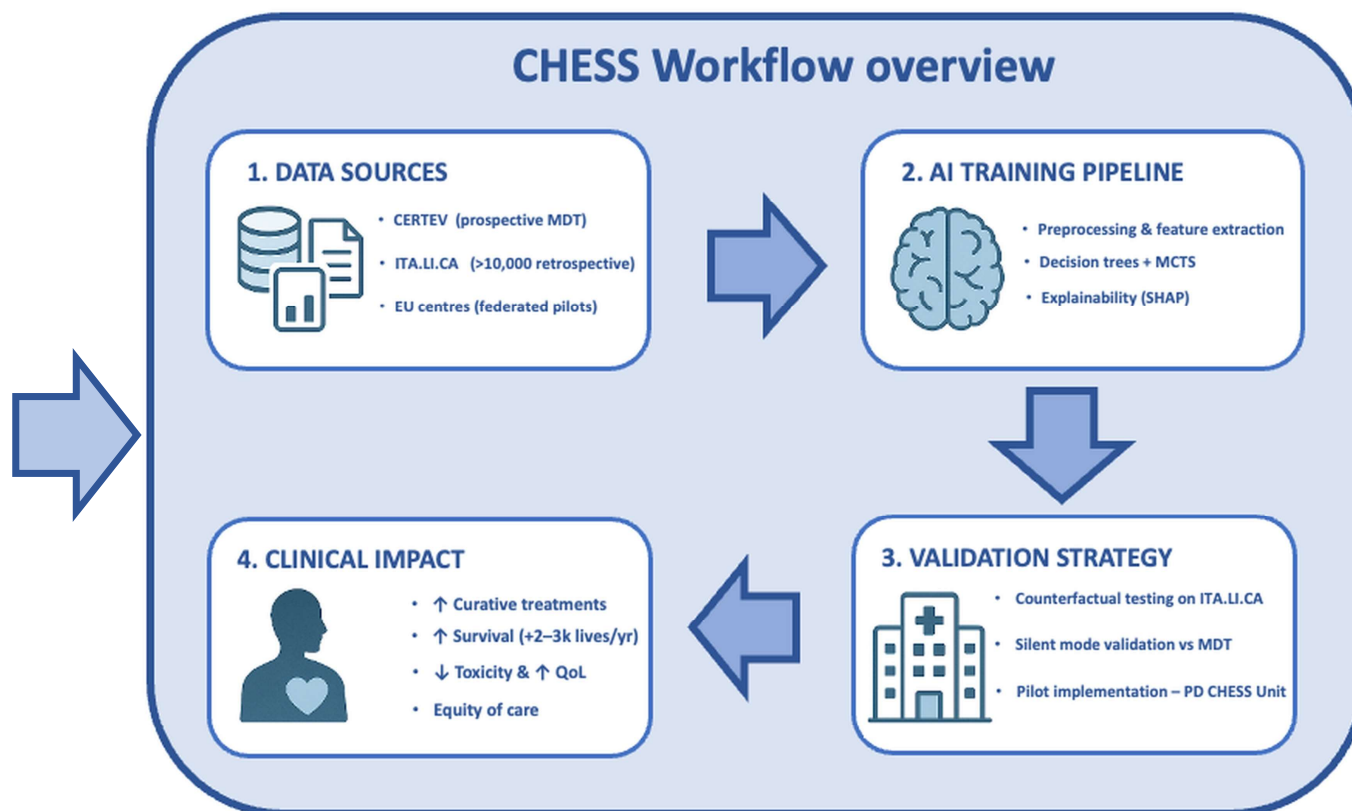
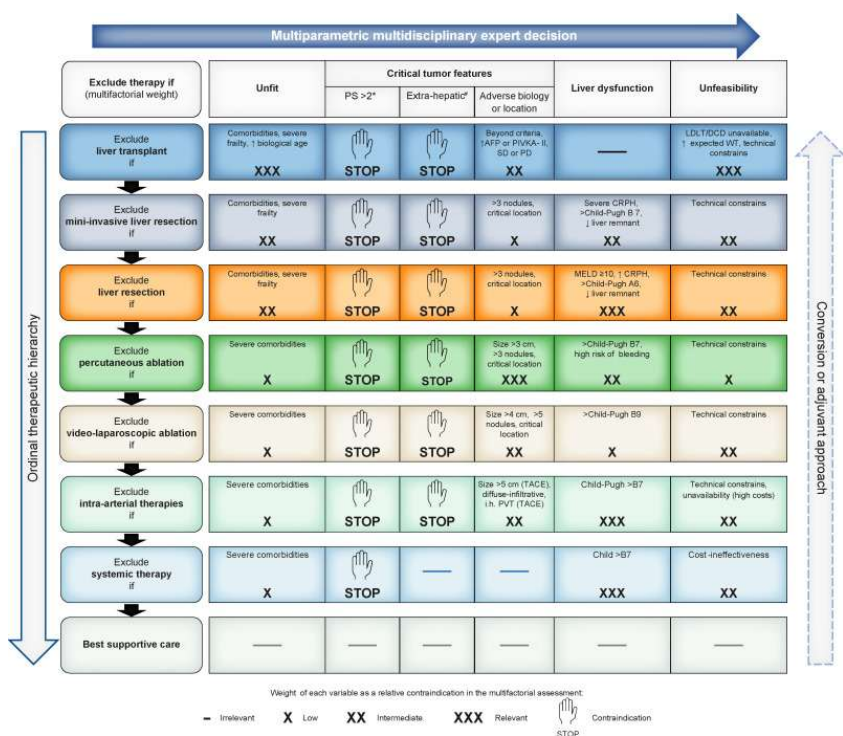


Ng et al. Trials (2023) 24:577. <https://doi.org/10.1186/s13063-023-07610-8>

The Heisenberg's uncertainty: the digital MTH-EtD proposal

The Clinician Helper Expert Strategy System (CHESS):

A "Strategic Game-Inspired" AI Copilot to Enhance Personalised Sequential Decision-Making in Hepatocellular Carcinoma



Multiparametric and Converse Therapeutic Hierarchy in HCC



- From pre-Ptolemaic to Ptolemaic era
Merits of Stage Hierarchy
- The Ptolemaic System
Boundaries of Stage Hierarchy
- The Copernican and Newton's evolutions
Multiparametric Therapeutic Hierarchy and expert MDT
- The Einstein's relativity
Converse Therapeutic Hierarchy
- The Heisenberg's uncertainty
 - Certainty of evidence is not dichotomic, is a continuum ...
- Uncertainty refers to individual and logistic complexities and should be always considered (by EtD tools and AI)