Positioning Therapies for Liver Cancers

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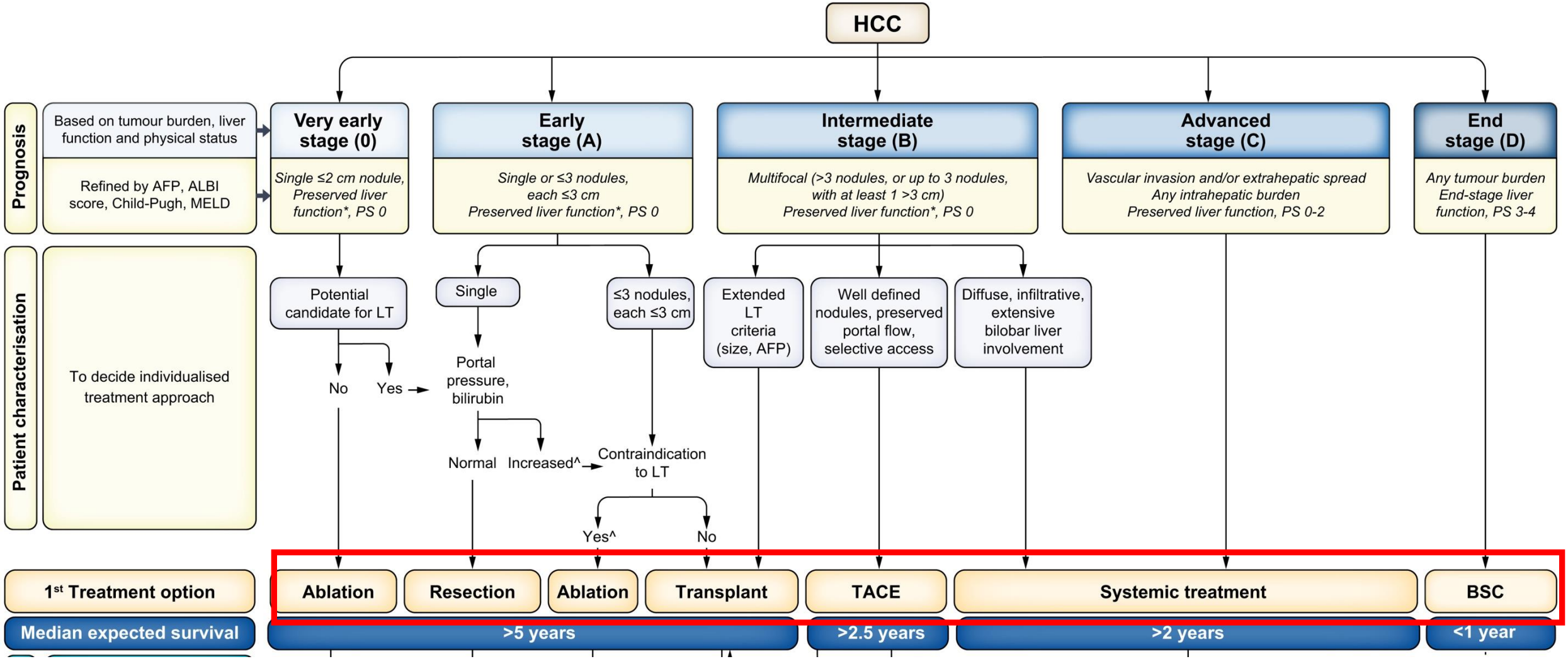
Disclosures

- I have no relevant financial disclosures.


HCC
Prognosis
Based on tumour burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
Single ≤2 cm nodule, Preserved liver function*, PS 0
Early stage (A)
Single or ≤3 nodules, each ≤3 cm Preserved liver function*, PS 0
Intermediate stage (B)
Multifocal (>3 nodules, or up to 3 nodules, with at least 1 >3 cm) Preserved liver function*, PS 0
Advanced stage (C)
Vascular invasion and/or extrahepatic spread Any intrahepatic burden Preserved liver function, PS 0-2
End stage (D)
Any tumour burden End-stage liver function, PS 3-4
Patient characterisation
To decide individualised treatment approach
Potential candidate for LT
No
Yes
Single
Portal pressure, bilirubin
Normal
Increased^
≤3 nodules, each ≤3 cm
Contraindication to LT
Yes^
No
Extended LT criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Median expected survival
>5 years
>2.5 years
>2 years
<1 year

Why This Matters to Your Practice

3rd
Leading cause of cancer death worldwide

#1
Cancer death cause in cirrhosis

Most
Patients first encountered outside specialty care

Stage
Determines survival dramatically

Early positioning determines survival.

Asrani SK, et al. Burden of liver diseases in the world. *Journal of Hepatology*. 2019;70(1):151–171. *(#1 cause of cancer death in cirrhosis; rising HCC incidence)*

Who Gets HCC? High-Risk Populations

Established Cirrhosis

Hepatitis C
Hepatitis B
MASLD ↑ rapidly
Alcohol-related

No Cirrhosis Required

Hepatitis B
(even without cirrhosis)
Advanced MASLD/MASH
(F3–F4 fibrosis)

The Surveillance Gap

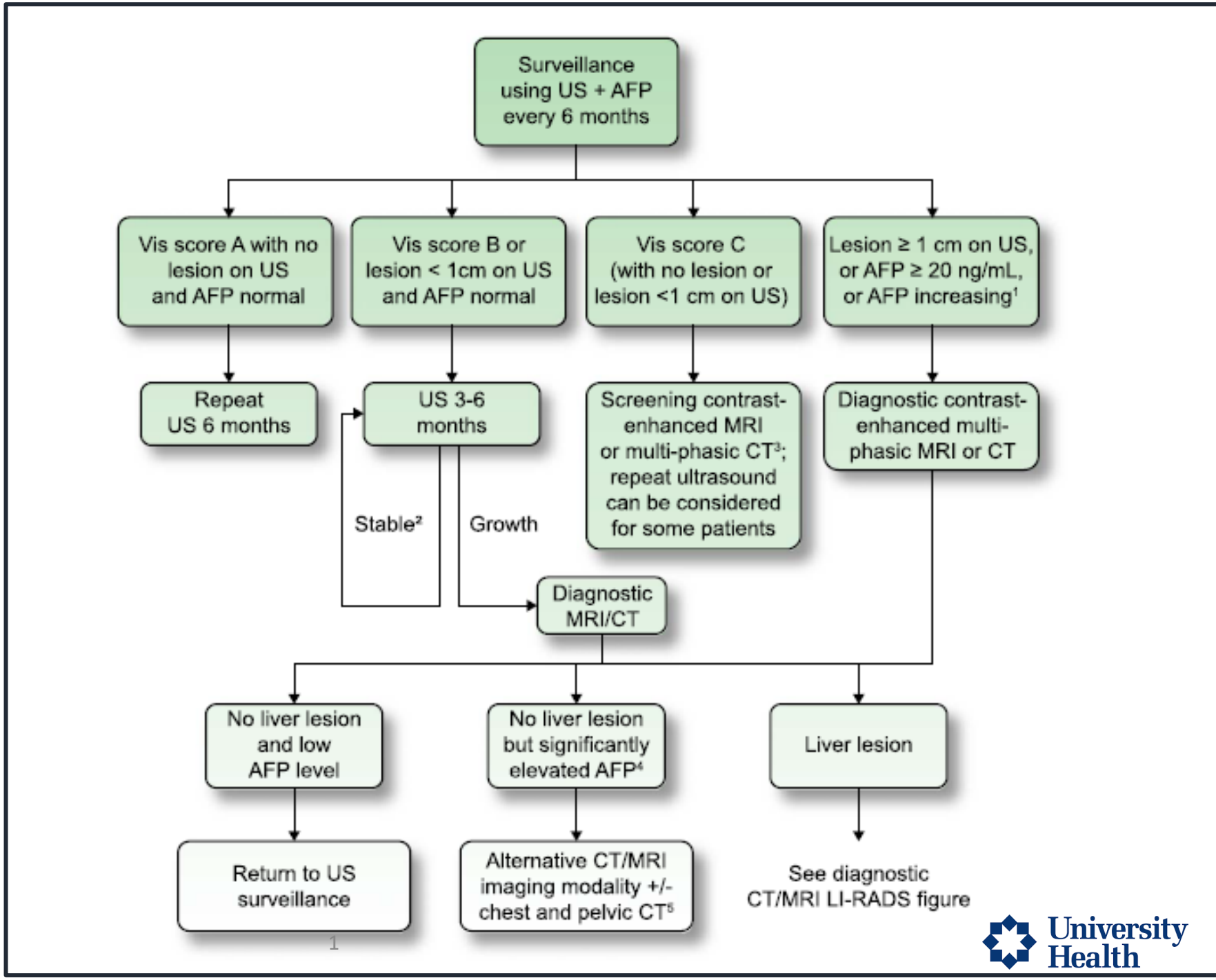
<25%

of eligible cirrhosis patients receive guideline-recommended surveillance

Marrero JA, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2018;68(2):723–750

Screening?

US+AFP
Sensitivity %63



AASLD, Hepatol 2023

University Health

Natural History Without Treatment

Median survival by BCLC stage — untreated

BCLC 0 (Very Early) — Median >5 years

BCLC A (Early) — Median ~36 months

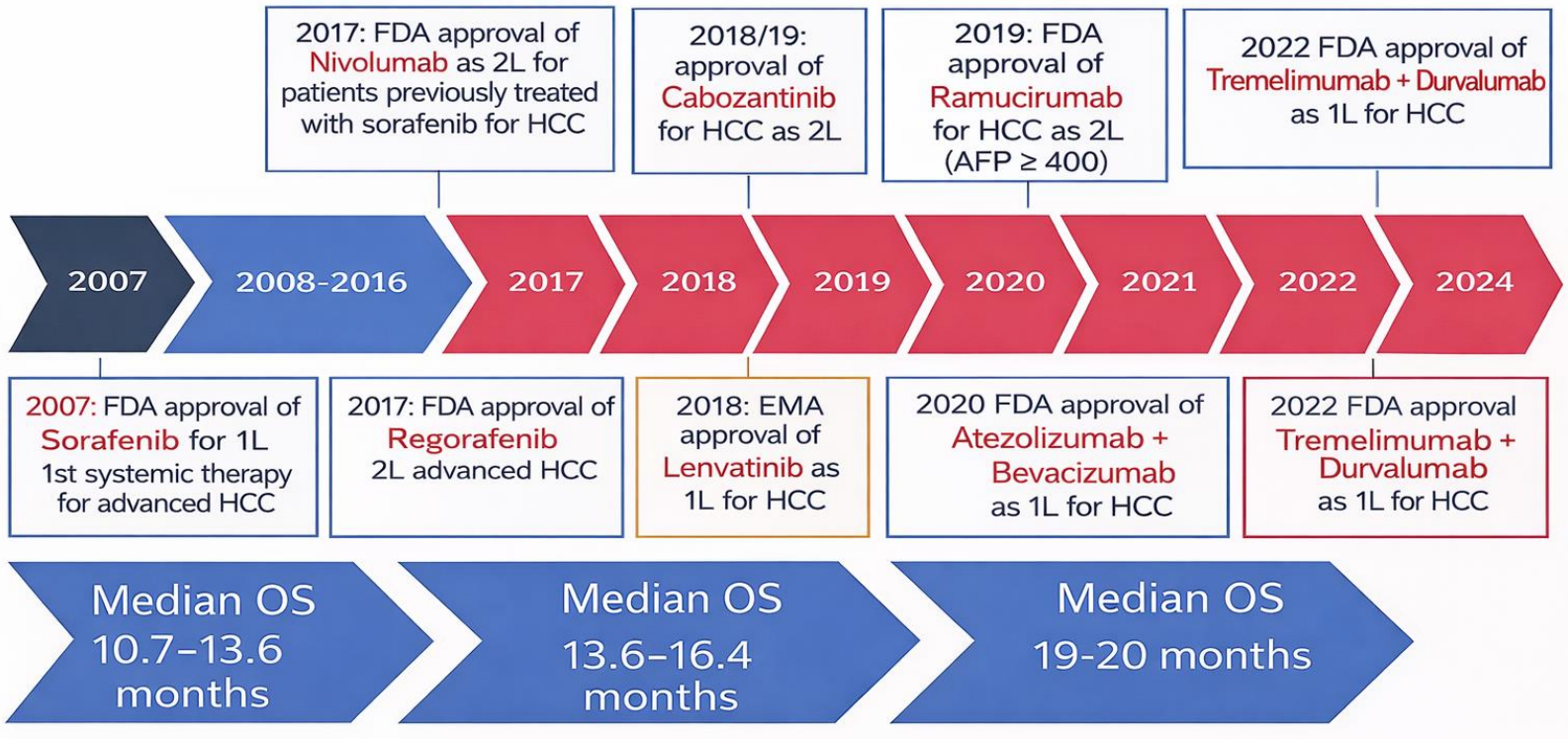
BCLC B (Intermediate) — Median ~16 months

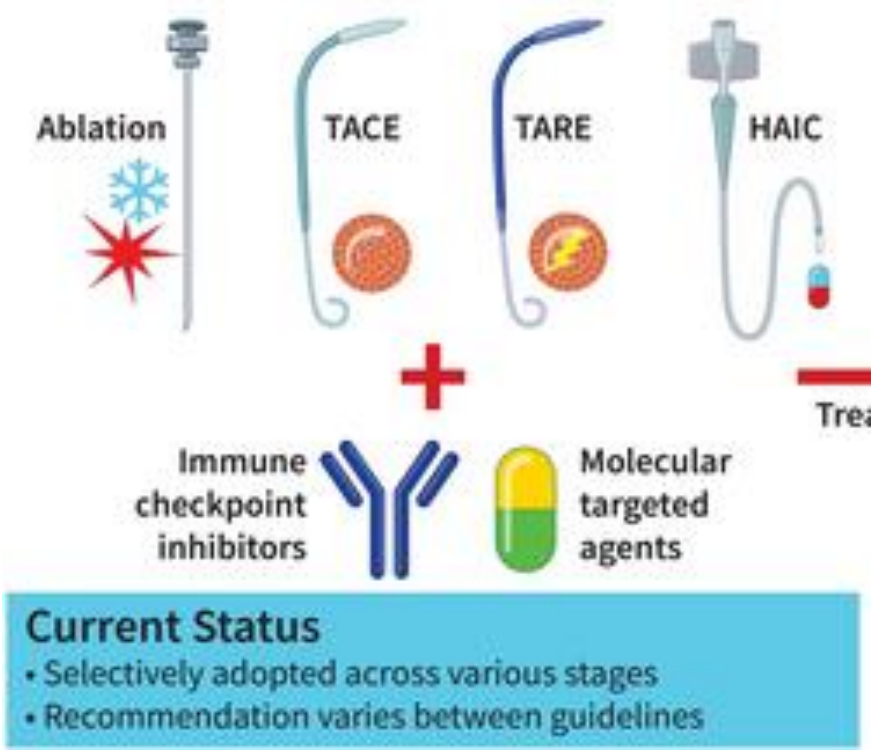
BCLC C (Advanced) — Median ~6 months

BCLC D — <3 months

Every stage earlier = months to years of life gained

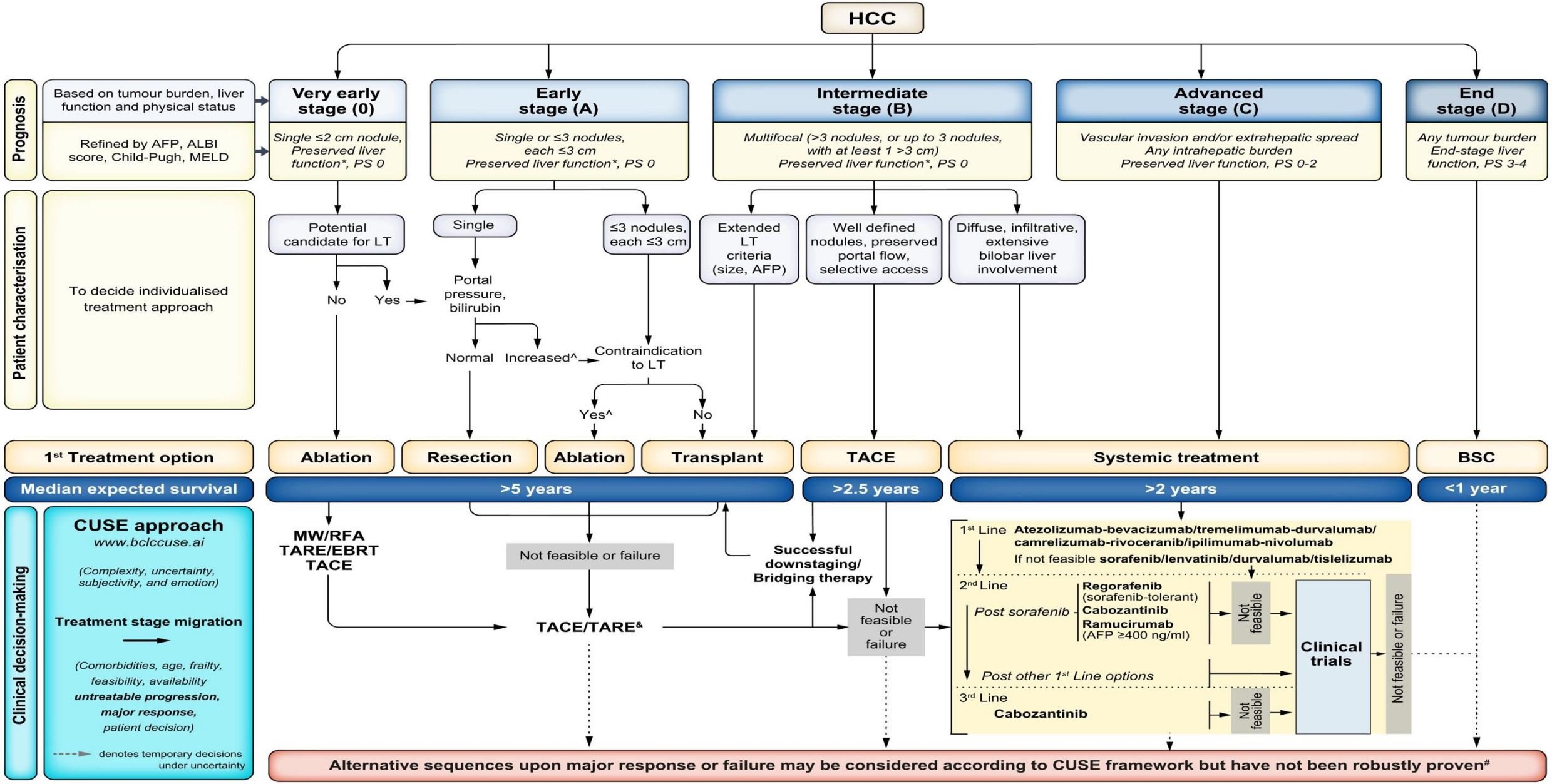
Advancements in HCC Treatment





Karan K, Vivek A. Saraswat. Journ of Clinical and Experiment Hepatol, 2025

BCLC Staging



Curative Intent Therapies — BCLC 0 & A

Resection

Who qualifies:
Preserved liver function (Child A)
Localized tumor, adequate remnant

5-yr survival: up to 70%

Ablation

Who qualifies:
Small tumors (<3 cm ideal)
Not resectable or patient preference

Comparable to resection <2 cm

Liver Transplant ★

Milan Criteria:
1 lesion ≤5 cm OR ≤3 lesions ≤3 cm
No vascular invasion or extrahepatic spread

Treats cancer AND cirrhosis

Refer early — transplant eligibility disappears quickly as tumor progresses

Reig M, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *Journal of Hepatology*. 2022;76(3):681–693.

Transplant Positioning

Key Concepts

Downstaging

Tumor too big for Milan? Locoregional therapy can shrink it INTO criteria

MELD Exception Points

HCC patients get extra MELD points to compete for donor organs despite preserved liver function

Transplant is cure!

Mazzaferro V, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New England Journal of Medicine*. 1996;334(11):693–699.

Locoregional Therapies — BCLC B

Goal: Disease control • Bridge to transplant

TACE

Transarterial chemoembolization
Most widely used worldwide
Multiple sessions common

TARE (Y-90)

Radioembolization (yttrium-90)
Fewer sessions, better tolerated
Useful with portal vein involvement
Can enable downstaging

Ablation Combinations

RFA/MWA + TACE combined
For intermediate-sized lesions
Decision made by multidisciplinary team

Note: Child’s Pugh B/C patients may not tolerate these procedures regardless of tumor burden

TACE vs Y-90: Practical Differences

Feature	TACE	Y-90 (TARE)
Mechanism	Ischemic (chemo + embolic)	Internal radiation (beta emission)
Sessions needed	Often multiple repeat sessions	Often 1–2 sessions (lobar/segmental)
Side effects	Post-embolization syndrome common (fever, pain, nausea)	Better tolerated; radiation pneumonitis rare risk
Portal vein thrombosis	Generally contraindicated	**Can be used**

Liver function determines tolerance, not just tumor size

Llovet JM, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma. *Lancet.* 2002;359(9319):1734–1739.

The Systemic Therapy Era — A Paradigm Shift

2007–2017
Sorafenib Era

Only systemic option
Median OS ~10–11 months
TKI mechanism

2017–2019
TKI Expansion

Lenvatinib
1st line, non-inferior
Regorafenib / Cabozantinib
2nd line options

2020–Present
IO Combinations

Atezo + Bev
Durva + Treme
Median OS ~19–22 months

Median OS nearly doubled compared to the sorafenib era

Kudo M, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma (REFLECT). *Lancet.* 2018;391(10126):1163–1173. **Finn RS, et al.** Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma (IMbrave150). *New England Journal of Medicine.* 2020;382(20):1894–1905.

First-Line Systemic Therapy

Atezolizumab + Bevacizumab

IMbrave150 Trial

PD-L1 inhibitor (atezo) + anti-VEGF (bev)
Child-Pugh A liver function required

⚠ **Endoscopy required first**
Bevacizumab carries variceal bleed risk

Durvalumab + Tremelimumab

HIMALAYA Trial (STRIDE regimen)

Dual IO: PD-L1 + CTLA-4 blockade
Child-Pugh A liver function required

✓ **No bevacizumab — endoscopy not required**
Option when varices are present or untreated

Both require: Child-Pugh A • ECOG PS 0–1 • No autoimmune contraindications • Adequate renal function

Finn RS, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma (IMbrave150). *New England Journal of Medicine.* 2020;382(20):1894–1905. **Abou-Alfa GK, et al.** Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma (HIMALAYA). *NEJM Evidence.* 2022;1(8).

Considerations on Immunotherapy

Other Disease Monitoring

Rheumatoid Arthritis
Psoriasis and Psoriatic Arthritis
Inflammatory Bowel Disease
Autoimmune Thyroid Disease
Multiple Sclerosis
Sjogren's Syndrome
Lupus

Side Effects

Rash
GI Symptoms
Endocrine Abnormalities
Pneumonitis
Fatigue
Weight Loss

Second-Line Therapy

After IO-Based 1st Line

Sorafenib / Lenvatinib / Cabozantinib

Principle: progression → switch mechanism. Liver function informs the decision.

Bruix J, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE). *Lancet.* 2017;389(10064):56–66.

Situations to Recognize

Portal Vein Thrombosis (PVT)

New PVT → could be tumor thrombus. Refer early.

Decompensated Cirrhosis + HCC

Child-Pugh C = no systemic therapy, no locoregional therapy eligibility

Frailty & Sarcopenia

Muscle wasting predicts poor treatment tolerance.

MASLD Without Cirrhosis

HCC in MASLD can present at advanced stage. No cirrhosis does NOT mean no HCC risk.

Bahl S, et al. Sarcopenia and frailty in hepatocellular carcinoma: impact on outcomes. *Journal of Hepatology*.2021;74(4):966–978.

Future Directions

LRT + IO Combinations

TACE or Y-90 combined with checkpoint inhibitors

Earlier IO Use

Trials exploring IO in adjuvant and peri-transplant settings

Biomarkers

Predictive biomarkers for IO response still limited

He MK, et al. Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus lenvatinib alone for advanced hepatocellular carcinoma. *Therapeutic Advances in Medical Oncology.* 2021;13:17588359211002301.

Key Takeaways

1. Early detection changes survival dramatically
2. Liver function drives every therapy decision
3. Transplant is oncologic therapy
4. Immunotherapy is the new first-line standard
5. Early referral prevents lost opportunities